The New England
Journal of Medicine

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Volume 235 DECEMBER 26, 1946 Number 26

PROBLEMS ARISING IN THE TREATMENT OF SYPHILIS WITH PENICILLIN

WILLIAM R. HILL, M.D.*

BOSTON

THIS report deals with the therapeutic pitfalls encountered in 125 patients with various types of syphilis who were treated with penicillin at the Massachusetts General Hospital subsequent to November, 1944. All these patients were hospitalized and treated for periods ranging from eight to fifteen days. Penicillin in aqueous solution was administered intramuscularly in doses of 20,000 to 40,000 Oxford units every three hours, day and night. The total dose was from a minimum of 1,200,000 to 2,400,000 Oxford units. Arsenicals and bismuth were not used concomitantly with penicillin, but in most patients with interstitial keratitis or neurosyphilis, fever therapy supplemented the treatment with penicillin.

PENICILLIN RESISTANCE

Late Syphilis

In this series the majority of patients with late syphilis who had exhibited persistently positive serologic reactions (Wassermann fastness) and who had received adequate treatment with arsenicals and bismuth before penicillin therapy was begun failed to show an appreciable reduction in the serologic titer. Occasionally, a negative serologic reaction was noted immediately following penicillin therapy. Re-examination some months later showed that the change was only temporary.

The results in the cases of acute interstitial keratitis treated with penicillin were unpredictable. Penicillin alone was administered to 3 patients in total doses of 1,200,000 to 2,400,000 Oxford units. This was combined with malaria therapy in 1 case and with typhoid vaccine to produce fever in another. Two patients who were treated with penicillin alone experienced favorable clinical results; no subjective or objective improvement was noted in the remaining 3. One patient, who improved clinically and in whom, after ten months' follow-up study, a serologic reversal was obtained, had been treated with a total dose of 1,200,000 Oxford units of penicillin alone.

*Assistant in medicine and in dermatology, Harvard Medical School; assistant physician and assistant in dermatology in charge of the South Medical Clinic (Syphilis), Massachusetts General Hospital.

Three patients who had advanced optic atrophy — 1 with congenital, and the other 2 with acquired syphilis — failed to respond clinically to a total dose of 2,400,000 Oxford units, which each received over a period of eight days. No improvement in the visual fields had been noted six months after therapy had ended. One patient with deafness due to involvement of the eighth cranial nerve was treated with 1,200,000 Oxford units but did not respond favorably.

None of the 5 patients with neurosyphilis with lightning pains showed any change in the character or intensity of the pains following treatment with a total dose of 2,400,000 Oxford units of penicillin. One patient who had neurosyphilis and gastric crises did not benefit when a total dose of 900,000 Oxford units was given intrathecally, together with 2,400,000 Oxford units by the intramuscular route.

O'Leary, Brunsting and Ockuly[1] reported no improvement in gastric crises, ataxia or incontinence in persons with neurosyphilis; nor was clinical improvement noted in their cases of early dementia paralytica in which penicillin alone was given.

Favorable results have been reported in late cutaneous syphilis.[2] Recently, however, I have had the opportunity of examining a patient with an extensive destructive gumma involving the center of the face, including the nasal septum, and hard palate who had received 2,400,000 Oxford units of penicillin before admission, without improvement. Therapy with induced malaria completely resolved the lesion.

Early Syphilis

We have noted no evidence of penicillin resistance in this type of case. Tyson,[3] however, reported the case of a colored man who had primary syphilis. The dark-field examination was positive. He was treated with a total dose of 2,400,000 Oxford units of penicillin intramuscularly in the course of four days. The penile lesion did not heal. *Treponema pallidum* was seen on dark-field examination of the lesion four months later. At that time, also, lesions of secondary syphilis were present and a

serologic test was reported as positive. Retreatment consisted of 600,000 Oxford units of penicillin, in addition to eight hours of fever therapy; this caused resolution of the lesions. Three months later, the serologic tests were reported negative. The lesson to be learned is that the time element (in this case, four days) is more important in cure than the total dose. The duration of penicillin therapy (four days) also appears to have been significant in Beerman and Ingraham's case[4] in which treatment failed. In both cases the time was too short to sustain a therapeutic blood level of the drug.

Limitations of Therapy

Relapse

The effectiveness of a new antispirochetal agent in early syphilis is judged by the incidence of relapse, both clinical and serologic, following its use. Relapse has been defined as either a persistent, rising serologic titer or clinical evidence of progression of the disease. Its implications regarding public health are obvious.

Among 75 patients with early syphilis treated at the Massachusetts General Hospital, 2 had serologic and 3 had clinical (mucocutaneous) relapses — a rate of approximately 7 per cent in patients followed for at least six months. One of the latter group, a woman five months' pregnant with secondary syphilis, had been treated with 1,200,000 Oxford units of penicillin. At the time of delivery of a full-term, normal-appearing infant, the mother's serologic reaction was positive although tending toward negativity. The serologic reaction in the infant was negative until the third month, when it became positive. At that time, both the mother and the infant presented cutaneous lesions suggestive of secondary syphilis. From the perianal lesion of the infant, material taken for a dark-field examination revealed *Tr. pallidum*. Progress after treatment with double the total dose for the mother — 2,400,000 Oxford units of penicillin — and a total dose of 1,200,000 units for the infant has been satisfactory. Beerman and Ingraham[4] reported a somewhat similar case in which the same dose was given in four days. This patient, who had not been cured of syphilis, had an infectious relapse and transmitted the disease to the infant about the time of delivery.

In a group of 27 pregnant women with early syphilis who were treated with penicillin by Ingraham and his co-workers,[5] the rate of clinical and serologic relapse was 11 per cent.

Moore[6] reported that the incidence of relapse when penicillin was administered alone was in direct relation to the total dose given by the intramuscular route in a period of seven and a half days. It was greatest with 60,000 units and least with 1,200,000. Relapse appeared to be more frequent after intravenous use than after intramuscular administration of comparable doses.

In a report by the Committee on Medical Research and the United States Public Health Service[7] on the treatment of early syphilis with penicillin, the lowest cumulative failure rate — 15 per cent at the end of eleven months' follow-up study — occurred following the administration of a total dose of 2,400,000 Oxford units. With a total dose of 60,000 units, the rate was 62 per cent.

In a series of cases of early syphilis reported by Moore et al.,[8] patients with seronegative primary syphilis treated with intramuscular penicillin showed a relapse rate of 3.2 per cent. The rate was 5.0 per cent in those with seropositive primary syphilis, and 9.8 per cent in those with secondary syphilis. Leifer[9] reported that 96 patients with early syphilis treated with a total of 1,200,000 Oxford units had a relapse rate of 9.6 per cent. Leifer's series also included 2 patients who had neurologic relapses. Although the seriousness of this complication was appreciated, it was not encountered in the series at the Massachusetts General Hospital.

The lowest incidence of relapse[8] and the most favorable serologic response was seen in a small group of patients treated with 60,000 and 300,000 Oxford units of penicillin, together with a known subcurative dose of Mapharsen. Similar results have been reported in patients treated with penicillin and bismuth.[7]

Observation of 69 infants treated for infantile congenital syphilis revealed serologic relapse in 5 patients, with clinical relapse in 2 of these cases.[10] Serologic relapse occurred in three to six months after treatment, and clinical relapse at six months.

Serologic and clinical relapse in the cases of early syphilis in this series was noted between the third and the ninth month, but the danger period extended to the end of the second year following the original treatment.

Reinfection

Reinfection as opposed to relapse is infrequent. Of 150 supposed reinfections, clinicians associated with the Central Statistical Unit agreed to fulfillment of adequate criteria of reinfection in only 2 cases.[7]

Although one case failed to fulfill these rigid criteria, it portrayed a frequent pitfall referred to as "pingpong syphilis" (Schoch and Alexander[11]), which occurs uniquely in penicillin-treated syphilis. A male patient was discovered to have a dark-field-positive chancre, for which he was given 2,400,000 Oxford units of penicillin intramuscularly. A month later, his wife developed a vulvar lesion. Her serologic reaction at that time was positive, but no dark-field examination was performed. Early in the next month she received 2,400,000 Oxford units of penicillin intramuscularly. Three weeks later the husband noted a penile lesion on the opposite side from the original chancre. Dark-field examination was negative at that time but was reported positive for *Tr. pallidum* a month later. It is reasonable to believe that the husband after infecting his wife was cured

of the disease by penicillin but became reinfected after his wife developed the lesion.

In both relapse in early syphilis and reinfection, retreatment should consist of double the previous dose or more, with the addition of arsenic and bismuth. For data on this phase, reference to a report of the Committee on Medical Research and the United States Public Health Service[12] is advised. The decision to retreat usually arises between the third and the twelfth month following the original therapy.

Reactions

Although the incidence of severe reactions is insignificant when compared with those attending routine treatment with arsenic and bismuth, reactions do occur among patients treated with penicillin.

Shocklike Reactions

The Herxheimer reaction was noted in 75 per cent of patients with early syphilis in this series. In such cases, within the first eight hours and most frequently after the second injection, a rise in temperature to from 100 to 103°F. occurs. The patient complains of chilliness, headache, backache and malaise. There may be an exacerbation of preexisting lesions. This does not call for discontinuation of therapy. The patient becomes symptom free in another twelve hours. According to Stokes, Beerman and Ingraham,[13] this reaction occurs in 20 per cent of patients with late syphilis who are treated with penicillin. It may be grave, as is evidenced in the report of Lentz and his group,[14] who observed threatened abortion in 2 pregnant women treated for early syphilis with penicillin. This occurred within eighteen hours after the beginning of treatment in one case and within forty-eight hours in the other. The drug was discontinued immediately but was resumed in full dosage in twenty-four hours, without recurrence. Lentz et al. believe that this type of Herxheimer reaction may be referred to as "placental shock." In another article, Ingraham and his associates[5] report that a patient with early latent syphilis in the fourth month of pregnancy aborted on the fourth day after the beginning of penicillin therapy. In this case, treatment was begun cautiously, with a low dosage of penicillin for the first three days. Goodwin and Moore[15] do not agree that the reaction was due to penicillin.

Leavitt[16] noted that of 21 pregnant patients treated with penicillin, 8 manifested symptoms of uterine activity, consisting of uterine cramps or bleeding, or both. In 2 cases, evacuation of the contents of the uterus occurred. In Beerman and Ingraham's[4] series, a patient had a miscarriage during the course of treatment, and in another case, it was necessary to stop treatment until the symptoms of threatened miscarriage had subsided some weeks later.

One infant with congenital syphilis suddenly experienced severe, nearly fatal collapse forty-eight hours after treatment had been begun.[10] Three infants died during or soon after treatment (twenty-four hours, seven days and nine days, respectively). All the infants were under two months of age and were in poor general condition. Two other infants died (five weeks and fourteen weeks, respectively) after penicillin therapy. Whether these deaths were due to penicillin, directly or indirectly, is not known. It is prudent, in the penicillin treatment of debilitated children, to employ considerable caution.[17]

The 2 cases of cardiovascular syphilis reported by Dolkart and Schweimlein[18] in which anginal symptoms appeared shortly after the beginning of penicillin therapy are examples of a therapeutic paradox — a shocklike reaction that occurs at times in other vital structures, such as the liver. In all cases in which the possibility of therapeutic shock may be anticipated, it is wise to reduce the penicillin dosage by three fourths to a half for the first forty-eight hours. This reduction may be compensated for by prolongation of the course of treatment. In the present series, untoward reactions were not observed in a patient treated with penicillin who had syphilis and hypertensive cardiovascular disease and who was decompensated, or in a person who had cardiovascular syphilis with aortic regurgitation.

Neymann and his co-workers[19] reported 2 fatal cases following the use of penicillin intrathecally. They stated that the route is dangerous if more than 30,000 units are injected and that the daily injection of this dose prolonged for more than five days is hazardous. Their patients who died following such treatment exhibited tenseness at first. This was followed by generalized muscular twitching and finally by severe convulsions.

In this series a patient developed postarsenical jaundice, from which he appeared to make an uneventful recovery. Three months later he returned to the hospital for study and was given 2,400,000 Oxford units of penicillin over a period of eight days. Soon, the jaundice reappeared. This was followed by a progressively fatal course. A post-mortem diagnosis of subacute yellow atrophy was made. The question whether the penicillin was responsible for death cannot be answered satisfactorily. In the presence of previous liver damage, however, penicillin should be employed cautiously if at all.

Sensitization Reactions

Only 2 patients in this series developed urticaria while undergoing penicillin therapy for syphilis. But according to Anderson,[20] from 2 to 5 per cent of patients treated with penicillin develop urticaria. This may appear on the first day of treatment or may not become apparent until several days after treatment has been completed. It usually develops during the second week. Occasionally, it is severe,

but in most cases it is mild and frequently disappears even if treatment is continued.

Another type of allergic response is a vesiculobullous or papular eruption, generally followed by desquamation. This also occurs in the first twenty-four hours. The continuation of therapy in these cases aggravates the disease.

Transient gastrointestinal reactions, consisting of nausea, vomiting and diarrhea, have been noted in syphilitic patients treated with penicillin.

The maximal dose of penicillin that can safely be given to man has not been determined. So far as is known, penicillin is not incompatible with any other antisyphilitic drug.

Public-Health Aspects

Masking of Syphilis

In 1 case in this series the treatment of gonorrhea with penicillin during the incubation period of syphilis masked the disease. The diagnosis of syphilis was delayed for six months, and during the interval the patient infected his wife. Walker and Barton[21] reviewed 8 cases in which patients with gonorrhea were treated with 100,000 Oxford units of penicillin — given in one day — during the incubation period of syphilis. Such a small dose of penicillin, although capable of curing the gonorrhea, is likely to suppress the primary and secondary manifestations of a concomitant early syphilitic infection but does not prevent recurrences. Under these circumstances, the patient is denied the benefit of adequate treatment for syphilis in the seronegative stage, in which the chances of cure are greatest, and the public is exposed to a definite source of infection. In most cases the patient's condition is diagnosed weeks or months later when he is seen with a clinical or serologic relapse.

Magnuson and Eagle[22] stated that, with the increasing use of penicillin for gonorrhea, it is probable that the number of aborted, delayed or symptomatically acquired lesions of early syphilis will increase. MacKenzie and Wrong[23] therefore advise the use of sulfonamides rather than penicillin in cases of urethritis in which a coincidental infection with syphilis is suspected. These authors noted that penicillin administered during the incubation period of syphilis in subcurative doses modified the early bacteriologic and serologic findings. In their cases the appearance of the chancre was delayed to from sixty to seventy days, rather than the usual twenty-six days, and the serologic reaction became positive in four to five months, instead of an average of forty-five days, from the date of the infection. They also found that when the primary lesion of syphilis appeared, it was necessary to perform repeated dark-field examinations before a positive result was obtained. Therefore, it seems necessary to subject patients receiving penicillin for gonorrhea to a six months' follow-up study for syphilis. Any patient who has gonorrhea and shows an early Herxheimer reaction,[21] evidenced by a rise in temperature after the first injection of penicillin, should be examined for syphilis.

Another pernicious habit concerns the blanket use of penicillin in mucocutaneous ulcerations, in which such treatment may mask the coincidental development of syphilis. A patient in this series had been treated for an ulcerative genital lesion by a physician with 600,000 Oxford units of penicillin, peanut oil and beeswax mixture intramuscularly, with no attempt to diagnose the condition by dark-field examination or pretreatment serologic reaction. This treatment, which was inadequate for early syphilis, was sufficient to render the dark-field examination negative for *Tr. pallidum* and probably delayed the development of a positive serologic reaction. To protect such patients and the community at large, it is necessary to accept the diagnosis of syphilis under these conditions and to offer treatment sufficient to cure.

Another case was that of a young woman with an ulceration of the lower lip who had been treated with penicillin troches. The medication caused the lesions to regress temporarily, but several weeks later, when the diagnosis was suspected, a dark-field examination revealed *Tr. pallidum*. A serologic test taken at that time was positive.

Lapse of Treatment

In general, experience with this group of patients revealed that case holding is far more difficult for penicillin-treated early syphilis than for patients treated under the arsenic and bismuth regime. Under the latter, the patient is satisfied that something positive is being done at each visit — namely, treatment. On follow-up study after penicillin treatment he is merely "looked at" and blood is drawn for a serologic test. This circumstance, together with the early favorable reports of the test, lulls him into complacency. One of the great advantages of the arsenic and bismuth regime, from a public-health viewpoint, was that patients with early syphilis received some treatment continuously during the first year and a half or two years of the disease, the time of greatest relapse.

The Returning Veteran

High on the list of problems in public health in the treatment of syphilis with penicillin will be the follow-up and case-holding system for the returning members of the armed forces who have been treated for syphilis with penicillin while in the service. The family physician will undoubtedly share in this aspect of the problem. He should therefore be acquainted with the following facts, if his patient and the community are to be protected.

All service personnel who have been treated for syphilis while members of the armed forces are informed before discharge what is expected of them in following up their treatment and are told where

this treatment can be obtained. They are instructed to present their separation-report leaflet to the physician of their choice, informing him that the type, amount and dates of treatment are on file at the state health department. This leaflet shows the results of serologic tests, including a report of the examination of the cerebrospinal fluid taken before discharge from the service. The treatment these patients have had is listed on Form 78A. If for some reason this form is not obtainable from the state health department, or if further information is desired, the physician can write to the Bureau of Medicine and Surgery, United States Navy, or to the Preventive Medical Service, Office of the Surgeon General, United States Army, in Washington. With this information at hand, the attending physician should be able to reach some decision on future follow-up study of the patient.

At the Massachusetts General Hospital, patients with early syphilis who have been treated with penicillin are seen for follow-up examinations (including at each visit a complete physical examination, with special attention to the skin and mucous membranes, and a quantitative serologic test) every two weeks for the first year. At the end of the first year, if there has been no clinical relapse and serologic tests are negative, another examination of the cerebrospinal fluid should be made. During the second year, the patient should be seen at least every three months. Attention is again called to clinical and serologic relapse, which is most frequent in the first two years after the initial treatment for early syphilis. At the end of the second year, assuming that all findings are negative, the patient is placed on a yearly follow-up basis for the remainder of his life; the wiseness of programs that advocate following the treated veteran for a maximum of only five years is doubtful. Again, assuming that the patient is progressing satisfactorily, an examination of the cardiovascular system, including roentgenology and fluoroscopy, is made five years after treatment has been completed. This entire subject, together with the action taken on it by the armed forces and civilian public-health authorities and with the part the civilian physician and the veteran himself play in it, has been reviewed in detail by Perkins.[24]

It is further realized that men and women returning from the service have a responsibility in this program that they may, for various reasons, choose to neglect. Although proper methods of handling this situation exist in the state and local departments of public health, the private physician is lost when the patient fails in his duty. In certain states and communities, however, the private physician can, by communicating with the department of public health, by telephone or in writing, obtain the services of a trained social worker in venereal disease, who will get in touch with the lapsing patient. In this capacity, the social worker acts as the private physician's confidential representative, urging the patient to continue under the care of his physician. Persons failing to respond to this approach should be reported to the proper state or local public-health department for more aggressive action.

Marriage

When should a person who has had early syphilis and who has been treated with penicillin marry? My policy has been to advise postponing marriage until two years after the blood serologic reaction had become negative, provided that during this interval the patient is free from clinical manifestations and exhibits a persistently negative serologic reaction. At the end of this probationary period a spinal-fluid test must also be negative. Anything short of this regime invites disaster.

Summary

Although many of the untoward results of penicillin therapy will be remedied as experience with penicillin increases, especially when more studies become available in which various combinations of other antisyphilitic drugs are used in conjunction with penicillin, therapeutic overenthusiasm on the part of the practicing physician must be tempered by the facts presented above.

It is the duty of the physician who treats syphilis to know the types of the disease in which results with penicillin are inconclusive, to understand such therapeutic pitfalls as lapse, relapse, resistance, reinfection and the problems of retreatment and to familiarize himself with reaction hazards. It is encumbent on him to protect the public health by encouraging the returning veteran to continue the splendid work that the armed forces have performed in the treatment of early syphilis and by advising against the ill timed marriage of patients who have been treated for early syphilis with penicillin. Finally, a high index of suspicion regarding syphilis will protect the practicing physician from unwittingly adding to the reservoir of hidden syphilis by administering treatment that may mask the disease.

520 Commonwealth Avenue

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THE MEDICAL-CARE PROBLEM IN THE UNITED STATES*

LOUIS H. BAUER, M.D.†

HEMPSTEAD, NEW YORK

I SUPPOSE that there is no problem quite so controversial in the United States as that of medical care. We hear a great deal of propaganda — in its modern connotation, not its original one. It is not information; it is information on one side, an attempt to sway people into changing their opinions, regardless of facts. The medical profession and the whole subject of medical care have been the object of considerable vicious propaganda of that order for the last several years.

It is quite true that medical care in many areas of the United States is not what it should be, and that it is susceptible of a great deal of improvement. Many things that are said about it, however, are definitely not true. Of course, those things are said with the idea of deluding the public, so that they will accept something quite foreign to the American idea of how things should be done.

One of the subjects most frequently discussed is the matter of Selective Service statistics. It is constantly stated that these statistics showed that American manhood is falling apart. The facts are that although 4,217,000 men were rejected, 582,000 of those were rejected for mental deficiency, including 250,000 illiterates, and about 701,000 for neuropsychiatric defects. The psychiatrists would be the first to admit that those men could not have been made fit for medical service, no matter how much medical care they received. Furthermore, out of the total number, there were those who were totally blind or totally deaf, as well as those without an arm or a leg.

Therefore, when the statistics are analyzed down to the last man, it is found that not over 15 to 20 per cent, and probably not even that number, could have been salvaged for the armed forces with any medical care. Most of those rejected who were given an opportunity to have the defects corrected refused. Furthermore, people fail to consider that the medical standards of the United States Army and Navy were the highest in the world. Men rejected by our forces crossed the line into Canada and were accepted. No one would say that the cadets at West Point and Annapolis were in poor physical shape. Yet the fact remains that not more than 40 or 50 per cent pass the physical examination for flying.

Many other charges are made that do not concern medical problems at all. For example, as I have pointed out before, there was a cartoon several years ago showing a woman in rags and a sad state of malnutrition, surrounded by children in a similar condition, and the cartoon was entitled, "These people need medical care." That was used as propaganda to overturn our system of medical care in the United States. The people portrayed needed a great many other things worse. If they had been properly clothed and housed and fed, they probably would have needed little medical care. The problem is really economic; it becomes medical because of the economic factors, and all the medical care in the world will not solve the problem. The cure of the evil is an economic one, which is the community's responsibility and not primarily that of the medical profession.

One of the points of the American Medical Association program is that people should have proper housing, clothing and food, and that they should obtain these on an individual basis whenever possible; when it is not possible — for example, if they are misfits in the community — the community must take care of them, and so on up to higher levels if the local resources are inadequate. Thus, again, a certain section of the population that is in need of medical care is eliminated if the problem is

*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 14, 1946.

†Member, Board of Trustees, American Medical Association.

considered from an economic rather than a medical standpoint.

Another aspect of medical care is that of public health and preventive medicine. Half the counties in the United States do not have a full-time public-health service. In other sections the department of public health is under political control, and there is no efficiency of administration. It would not be feasible, of course, for every county in the United States to have a full-time public-health department. Indeed, there are five counties in the United States with only five persons per square mile; they could not afford it and would not need it. But neighboring counties could join and form a district health department, with a traveling health service. This could be done in most states within their own economy. If state funds are lacking, there is a legitimate opportunity for the federal government to help, leaving the control of the situation in local hands.

It is much better to prevent disease than to cure it after it has started, and the control of many diseases is dependent on the quality of public-health facilities, of sewage and mosquito control and of water and milk supplies. Some of the diseases can be entirely eliminated by proper public-health measures. Again, there is no necessity for pouring in medical care.

The shortage of physicians in certain areas is widely discussed. The doctor does not settle in a certain community primarily because there are not facilities for him to bring up his family and educate his children, or for competent practice. He has been trained to practice a high type of medicine, and when he goes to a community and finds no adequate facilities he either leaves or remains and practices poor medicine, which is even worse. The solution is the provision of hospital and diagnostic facilities in these areas. That approach is the main substance of the Hill–Burton Bill in Congress — providing such facilities throughout the country where they are not now available, the states retaining control over these institutions constructed with federal money. In some areas the lack of medical care will thereby, to a certain extent, be solved; in others it may be necessary to provide a subsidy for a physician to go to an area because of the small number of patients to be cared for. This problem can be solved through voluntary agencies.

Medical care has become more expensive, I believe, primarily because of the increased science that has developed. Seventy-five years ago, medicine was not a science but an art; it is now an art, as well as a science. There are those who wish to throw the art out the window and make medicine 100 per cent science, but the result would not be satisfactory. There is still the individual touch in medicine, as well as the effect. You men know, as well as anybody in the world, that the treatment in two cases of pneumonia cannot be identical merely because the diagnosis is the same. Psychology is involved in the treatment of every patient — in the so-called "doctor-patient relation," which is one of the reasons for the success of the American system of medicine, preventing the doctor from being exclusively scientific and the patient from being merely a case number.

The increased expense is not so much in the care that the physician gives — he is paid little more than he was a generation ago for a house call or an office visit; the cost is in diagnosis. The doctor must have expensive pieces of apparatus, as well as complicated procedures, to practice competent medicine today. He must have equipment for x-ray films, electrocardiograms, blood chemical studies and so forth, all of which cost the patient money. It is those matters that need attention and whose solution will be aided by some such means as the Hill–Burton Bill.

One other important measure is in insurance, about which a good deal is heard at present. You are all familiar with the proposal now before Congress, with hearings before the Senate Subcommittee on Education and Labor, the Wagner–Murray–Dingell Bill calling for compulsory health insurance. Organized medicine has sponsored a voluntary program. Certain members of the committee, Senators Murray, Wagner and Pepper, assert that the voluntary system will not work. They cite reasons, every one of which is susceptible of overturn. America is undoubtedly the best insured nation in the world, from every aspect. The American people are insurance minded, but they must be sold on the idea of insuring their health. I understand that it took fifty years to make the idea of life insurance successful. I do not mean to intimate that it will take fifty years for voluntary health insurance to succeed. In those days, nobody knew anything about the types of insurance that could be obtained. At present, it should be comparatively simple to sell health insurance, but it must be made available.

There are two types of hospital insurance — that provided by the Blue Cross and that sold by various commercial companies. The Blue Cross alone has somewhere around 22,000,000 people insured, and the number is going up week by week; in fact, every time I speak on the subject I have to amend the figures, so that I am not sure that 22,000,000 is correct at the present time. And there are many more who are insured for hospitalization through insurance companies.

Then, too, people are carrying all sorts of health and accident insurance. Probably 30,000,000 in the United States have some form of protection against illness. Not all of it is the same. Some of it is complete, and some of it covers emergencies; some of it covers surgery and obstetrics, and some of it covers hospital and medical care; some of it is commercial insurance; some of it is industrial insurance;

and some of it is carried in the plans sponsored by the medical societies. It is interesting to note that there is an increase of 114 per cent in the number of people insured under the last system alone, which shows that this idea is growing. It has been slow, of course. And that is one thing that must be admitted when the voluntary program is attacked. But I think that it is wise to go slow.

The American Medical Association was roundly censured in many quarters when the first approval was given to voluntary medical insurance because many people believed that the American Medical Association should advance an overall plan covering everybody in the United States. Nobody knew what was wanted. There was no actuarial background. No one knew how the medical profession or the public would react. Consequently, if a plan were developed and sold over the United States, the thing would have been killed years ago; it could not have worked. Accordingly, it was considered better to experiment and to start in small areas, accepting what was good and rejecting what was bad. There has been experimentation over a period of years, and we are beginning to know what is acceptable and what is not acceptable. As a result, order is beginning to come out of chaos, and as you probably know, the American Medical Association has just established a Division of Prepayment Medical Care and Insurance in the Council on Medical Service at headquarters in Chicago, and there has been formed an independent organization, Associated Medical Care Plans, which takes in all the plans that sell insurance, provided that they meet certain specifications set up by the Council. The idea is to make these plans uniform, so far as possible, and to have reciprocity among them so that a person moving from one state to another will not lose his insurance but may transfer to the plan in another state. Organizations having a national payroll with employees in New Hampshire, Massachusetts, New York, Pennsylvania and other places do not have to go to half a dozen different places to insure employees. They can go to one central agency, where they may be insured in different organizations. General Motors Corporation, for example, is not willing to insure its employees in New Hampshire for medical care if it cannot do the same thing for its employees in another state. It is essential that these plans be available nationally, and some arrangement should be made whereby they can be sold nationally, even though they are actually sold by different companies.

Another criticism leveled at voluntary health insurance is that few of these plans give complete medical care. That is true. The reason is that most of the plans that started out with complete coverage were unsuccessful because the public was not interested in an illness of three, four or five days; they are interested in the expensive type of illness and hospitalization, such as operation or delivery. That type of insurance is incorporated in most of the plans, and many of them are adding medical care in the hospital — that is, the patients are protected for surgery, obstetrics, and if they have an illness that requires hospitalization they are protected for the medical care while in the hospital. It has been interesting, in New York, at least, to note that the people who have been carrying limited insurance say that this increased policy for medical care in the hospital can be sold to holders of surgical and obstetric insurance much more easily than to people with no insurance at all. In other words, the former have become more insurance minded. They see the benefits and want to extend them. The policy that will ultimately be more or less universally sold will probably cover surgery, obstetrics and medical care in the hospital. Eventually, complete medical care in the office and the home may be included, but that will take time. That is the least important, because the greatest part of the problem will have been solved if the economic situation is improved, if diseases are controlled and eliminated by proper preventive medicine and public facilities, adequate diagnostic aid and hospital facilities and if protection against the costs of surgery, obstetrics and hospital medical care is provided.

The Wagner–Murray–Dingell Bill proposes a system of national health insurance, and we are told that this is not socialized medicine. In fact, I believe that President Truman, in his message on health, made that statement about five times; I do not know how many times Senator Wagner made the same statement when he was discussing the introduction of his bill to the Senate. "Methinks, the lady doth protest too much," as Shakespeare said. It certainly approaches socialized medicine; it is political medicine, anyway, which is worse. The Government collects the money and pays it out. The Government prescribes the regulations under which physician and patient must act, determines who is a specialist and, in certain instances, even decides who can have a specialist. That part of the bill pertaining to specialists states that the practitioner in charge of the case may summon a specialist, and the patient has no voice in the choice of the specialist. If the patient desires a specialist, he can make application to the nearest governmental agency for the specialist.

Senators Wagner, Murray and Dingell say that there is a free choice of physician. It is a free choice, if the physician agrees to take part in the plan, but not otherwise. Also, a physician can be chosen provided that his panel is not already filled, for the Bill limits the number of patients that a doctor may have. It is free choice, provided that the majority of physicians do not elect to be paid on a capitation basis. I see no possible way of having that without allotting people in a certain area to a certain doctor, which would not be free choice.

Even Mr. Altmeyer, in his cross-examination, had to admit that the choice was limited. He also said that if the physicians in a community did not agree to serve under the plan, the Public Health Service would send doctors into the area to practice medicine. That is how much the free choice amounts to.

The statement is also made that organized medicine is unfair when it claims that this is the first step in national socialization. A glance at the background is sufficient. What happened in Germany? The Germans had compulsory sickness insurance. What is happening in England? They are socializing all their public utilities, even the Bank of England. In 1938 or 1939, the year that the American Medical Association met in Atlantic City, a senator from Illinois came directly from Washington and asked permission to speak to the House of Delegates. That was granted. He made the following statement:

> We know nothing of patient, don't recognize its existence. It is your creation. We recognize an instrument called citizen, who is essential to the welfare of government.

Most of us were brought up to believe that the state was for the welfare of the citizen. One can find similar words about the citizen and the state in *Mein Kampf*, and yet the senator's statement has never been denied by anybody in Washington.

There are other shortcomings in the Bill. Compulsory insurance will be extremely expensive; the medicine provided will be anything but free. This Bill does not mention how the money is to be raised. That, of course, was done for a specific purpose: to get the bill into the hands of Senator Murray's committee. If taxes were mentioned, it would have to go to the Finance Committee, of which Senator George is chairman, where it probably would have received a frosty reception.

The money will have to be raised somehow. President Truman mentioned a 4 per cent tax, up to $3600, for each employed member of the family. If two people in the family received $3600, they would have to pay $288 for medical care. That is an extreme case, it may be said, because many people are in the lower income brackets. But that is not necessarily making the outlay of a family smaller, because when there are more people in the same family working, then the net cost will be higher. It is estimated that approximately four billion dollars, which is stated to be the present cost of medical care in the United States, can be raised by taxes. In my opinion, fourteen billion dollars would probably come nearer the actual figure if such a vicious scheme as this were adopted. We do not know how many bureaucrats would be given jobs if the bill went into effect, but at least 300,000 to 400,000 would undoubtedly be employed. In England, they have two nonmedical employees to one physician; and, in the extravagant way we do things in this country, there would probably be three or four to one. That army of people would have to be taken care of before any poor patient got a doctor. Inspections would be necessary everywhere. A bureaucratic government cannot be run without red tape — it thrives on it. The experiences of the depression should be remembered. In New York the Emergency Relief Administration prescribed regulations whereby doctors had to ask permission to visit a patient. They could go and make an initial call, and whether they got paid for it or not, they had to estimate the number of calls necessary for them to make on that patient, as well as giving the diagnosis on the patient, all the information being submitted on a postal card, mind you. If they found that the patient had complications, they had to get extra permission for three or four more calls. They were also told what to prescribe and what not to prescribe. Certain things were too expensive, and the government clerk was the one to prescribe, not the doctor. All these uplifters say that no interference in the practice of medicine is intended in the bill. Why was there interference by the Emergency Relief Administration during the depression? We can expect nothing different. It will be the same thing, only more so. It is simply the initial attempt on the part of a certain group to make this a totally socialist government. The next step will be easy.

There are one or two other matters in this bill that I should like to mention. A so-called "advisory council" is emphasized as being quite important. It will have sixteen members, I believe, who are to be appointed by the Surgeon-General of the Public Health Service. These names must be selected from panels submitted by professional and other societies. But the board has no authority. It is advisory only. Furthermore, do you think for one minute that the Surgeon-General will appoint to the board people he knows are going to disagree with him? Of course not! That board will be a sounding board; that is the only relation that it will have to a "board," in my opinion. Local boards in the various states and communities will actually run the practice of medicine.

It is all very well to say that this is not socialized medicine, that the patient will have free choice and that people will get medical care that was not previously available. It *is* socialized medicine. Some people may get medical care that they have never had before, but it will be inferior. In all countries where the government has taken control over the practice of medicine, the medical care has deteriorated.

Senator Pepper said that he wished the people would get as stirred up about the 600,000,000 man-hours lost from ill health as it did about the hours lost by strikes. It might be well to consider what has happened in other countries in that regard.

When compulsory insurance was developed in England, it was expected that the sickness rate would go up initially, because people would go to

a doctor who could not have afforded it previously, and that the costs would be increased for a while. Then the rate was expected to come down, because the patients would go to a doctor earlier, would not be sick so long and many conditions that they might otherwise have had would be prevented. The rate never did come down, however — in fact, it is still going up. Why? Because it encourages malingering. The number of man-days lost in the United States is 9 per man. In England, before the compulsory sickness insurance went into effect, it was approximately 11; it is now between 14 and 15. In Germany, before compulsory sickness insurance was adopted, it was around 14, and it went up to 28. Consequently, the problem of man-hours lost will not be solved by compulsory sickness insurance; it will be increased rather than decreased.

We all want more medical care, but we want it to be of a high quality. We believe that the program of the American Medical Association, which was released in February, is going to solve that.

The economic aspect of medical care was discussed above, as were preventive medicine and public-health service. Increased aid to the prospective mother is also a necessity. Adequate care in childbirth and proper nutrition to prevent disease in the child should be available on an individual basis, and if the patient is unable to pay for it, help should be given on a community basis, with Federal aid, if necessary, the doctor-patient relation being preserved.

Another point is a proper program for the veteran. I am glad to say that the present officials of the Veterans Administration are anxious to see the veteran taken care of in his own community by his own doctor, and that so far as possible, they are endeavoring to complete this program. They have already worked it out in several states, and they are now in the throes of making arrangements with New York; I hope that you will do the same here — that is, that you will make arrangements with the Veterans Administration on a reasonable basis to both sides, so that the veteran can be taken care of by you in his own community and not be sent to a public institution, unless he has some chronic disease.

Another point is that of research, which, it is generally agreed, should be extended. We are perfectly willing to have Government aid in the matter of research. We want it controlled by a scientific board, and not by a politically appointed director. One should not forget the aid given by the various philanthropic associations, such as the National Tuberculosis Association and the National Foundation for Infantile Paralysis, all of which are performing an excellent service and whose work would be cut off by any national program, making it that much more expensive, because those agencies did it purely on a voluntary contribution basis. One improvement could be made: the organizations should not have a dozen drives each year but one drive for all of them, the money being divided in the proportion actually needed.

Another important factor is education. By education, I mean that not only of the public, but also of the doctor, who is often not informed in these matters. If the average physician is asked whether he is against the Wagner–Murray–Dingell Bill, he will say "Yes." But, if he is asked why, he cannot explain. But physicians must know why they are against it, because the patients are interested. After all, the patient is the one who will decide whether or not the United States is to have socialized medicine; the medical profession will not decide the question. And, the public will get what it wants in the long run. But I cannot believe that the public knows what costs are entailed and what poor medical service will be provided under the proposed national health legislation. And you, gentlemen, must be the ones to tell them about it. Often, the public is not even aware of the facilities that are available.

During the hue and cry when the first Wagner–Murray Bill was introduced, the Medical Society of the State of New Jersey, asked, by way of radio, public speakers and the press, that any person in New Jersey who could not obtain medical care communicate with the Society or one of its county societies, the care being guaranteed. There were only 127 people who said that they could not obtain adequate care, and every one of these could have obtained medical care but did not know how. It is therefore a matter of educating the public of the ways available.

A fact that I have stressed many times and shall continue to stress is that there should be more interest in the county societies. I do not know the situation in New Hampshire, but if it is like that in the rest of the country, the county society is not active and the meetings are poorly attended. It is highly essential that the county society be the activating force in all these matters; otherwise, we are defeated before we start. The physician must be the engine in this whole matter, and he needs the backing of his county society. We must stimulate interest among the members of the medical societies to come out and take an active part and study these questions and know what they are all about, so that when they are called on to discuss them publicly or with the patient individually, there need be no fear of what the result will be.

RECENT ADVANCES IN THE CARE OF THE SURGICAL COMPLICATIONS OF DIABETES MELLITUS*

LELAND S. McKITTRICK, M.D.†

BOSTON

MUCH has already been written on the factors involved in the care of the surgical complications of patients with diabetes mellitus. The purpose of this paper is not to review the entire problem but rather to consider the effects of many recent advances in medical science on the care of these patients. I shall confine my remarks to the consideration of the surgical problems.

It is difficult to evaluate the factors that have improved the care of poor-risk and elderly patients in recent years. The security of all patients undergoing surgical procedures has been aided immeasurably by more careful and deliberate preparation for operation; an increasing understanding of fluid balance; parenteral feeding, including the vitamins, whole blood and plasma transfusions; the use of intestinal antiseptics in preparation for resection of the large bowel; and early mobilization. These benefits are shared alike by patients with and without diabetes. It should never be forgotten, however, that the diabetic patient must be evaluated in terms not only of his general and local surgical condition but also of the diabetic state and the facilities at hand to control it before and especially after operation. Increasing experience has convinced me that diabetes mellitus is no contraindication to any surgical procedure whose indications are clear, provided always that the medical, surgical and hospital teamwork is such as to ensure efficient, co-operative care of the patient's metabolic disturbance.

If possible, surgical emergencies are to be avoided. In a patient whose general condition permits the procedure, an operation for gallstones, interval appendicitis, hernia and the like is advised as soon as it can be done under conditions likeliest to assure a safe convalescence.

This discussion chiefly concerns two conditions that are not limited to patients with diabetes but that present particular problems to such patients — operations for which account for over two thirds of the surgical procedures carried out on the diabetic patients at the New England Deaconess Hospital. These conditions comprise infections of the skin and subcutaneous tissue, especially carbuncles, and gangrene and infections of the lower extremities. It is gratifying that the medical advances of the past five years have proved particularly helpful to patients with these complications.

*From the New England Deaconess Hospital.
Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1946.

†Associate in surgery, Harvard Medical School; surgeon-in-chief, Palmer Memorial Hospital; surgeon, New England Deaconess Hospital; visiting surgeon, Massachusetts General Hospital.

Carbuncles

The 7 deaths among the 95 patients with carbuncles operated on between 1928 and 1941 give no concept of the seriousness of this problem in terms of loss of time and suffering of the patient. It is too early to evaluate the full benefits that penicillin in adequate dosage offers to the patient with a carbuncle. Experience to date at the New England Deaconess Hospital, however, has been most gratifying. We have seen the large, brawny, indurated, painful lesion characteristic of the earlier stages of a large carbuncle completely disappear after control of the diabetes and the daily injection of 100,000 to 300,000 units of penicillin for seven to ten days. Similar lesions in a more advanced stage have resolved into small local painless fluctuant areas 2 or 3 cm. in diameter and have healed promptly after local incision; these lesions, at the worst, would have resulted fatally in 5 to 10 per cent of cases prior to the use of penicillin and, at best, would have cost the patient weeks of hospital care, as well as a wound requiring months for final healing.

To date the cases have been too few and the experience too limited to warrant any definite conclusions. It is adequate, however, to establish a working basis for the management of this type of lesion.

On the basis of this experience any diabetic patient with an early carbuncle is regarded as an emergency and is immediately admitted to the hospital. The diabetes is carefully treated, and daily injections of 300,000 units of penicillin are given in eight equally divided doses until the lesion is operated on or has resolved.

It is to be expected that the greater part of the cellulitis will either disappear completely or leave a broken-down central area that is probably best treated by a small incision, release of the fluid, packing with gauze for twenty-four to forty-eight hours and allowing the skin edges to fall together. This method of handling the small residual cavity has in this limited experience been more satisfactory than attempts to control it by aspiration.

It is quite possible that the small carbuncles that fail to resolve completely and in which necrosis of skin occurs are best treated by excision and early skin graft. If the experience of the past two years is any guide for the future, the extensive operations for large carbuncles previously seen will seldom, if ever, be necessary, except in the badly neglected case.

At present the hospitalization of every patient with a carbuncle is strongly favored, with the parenteral use of penicillin rather than local injection or oral administration.

Leg Lesions Requiring Major Amputations

In 1934 McKittrick and Pratt[1] carefully analyzed the 57 deaths that had occurred at the New England Deaconess Hospital following operations for lesions in the lower extremities in 622 patients with diabetes mellitus. At that time it was suggested that if some means could be found to control the ever-dangerous infection, the mortality following amputation for gangrene should approximate 5.3 per cent. In the series of operations done between 1923 and 1942 the mortality after amputations through or above the mid-lower leg in 609 cases was 14.1 per cent, whereas that following major and minor amputations in 1036 cases was 9.7 per cent (Table 1). It is interesting to compare this with the results during the past five years when these patients had the benefit of the sulfonamides and of penicillin (Table 2).

TABLE 1. *Amputations of Lower Extremity in Diabetic Patients (1923–1941).*[2]

OPERATION	NO. OF CASES	NO. OF DEATHS	MORTALITY
			%
Amputation of one or more toes	356	8	2.2
Amputation of one or more toes, followed by major amputation	71	7	9.9
Amputation through or above mid-lower leg	609	86	14.1
Totals	1036	101	
Average			9.7

It is gratifying to note the drop in the mortality after all amputations, from 9.7 per cent to 2.6 per cent, and to observe how closely the mortality of 4.7 per cent for major amputations approximates that of 5.3 per cent suggested ten years previously. This remarkable improvement is considered to be of particular significance, since during this period there have been no important changes in the surgical management of these cases, except those made possible by an increasing ability to eliminate infection as a deciding factor in the type of operation to be carried out. The surgical technic, the principles of amputation, the anesthesia and to a large degree the personnel* have remained unchanged.

TABLE 2. *Amputations through or above Mid-Lower Leg (1941–1945).*

YEAR	NO. OF CASES	NO. OF DEATHS
1941	42	1
1942	46	4
1943	44	0
1944	37	2
1945	43	3
Totals	212	10 (4.7 per cent)

We continue to favor the supracondylar amputation, which is regarded as the easiest, safest operation and the one likeliest to heal promptly without complications. Amputation through the lower leg and the Gritti–Stokes operation are reserved for selected cases. Guillotine amputation through the lower leg for patients in poor condition and with extensive spreading infection is now rarely required because of the effectiveness of penicillin.

Lesions of the Feet Requiring Minor Amputations

The improvement in mortality is not the only benefit that these patients have derived from penicillin. In previous years, experience had repeatedly shown the dangers of carrying out local operation through or near an area of infection in a pulseless foot with poor collateral circulation. It was also apparent that a closed amputation carried out above the infected area usually resulted in satisfactory healing, even though there was little apparent arterial supply at the level of the incision. It therefore seemed only reasonable that if invasive local infection could be eliminated, many more conservative operations could be carried out with safety and with a reasonable chance of success.

The sulfonamides gave protection against certain streptococci but seemed of little help in eliminating the hazards of the more frequent staphylococci. It was therefore not until early 1944, when penicillin began to be available, that it seemed quite possible that operations could be carried out on certain of these patients with reasonable assurance that the site of amputation could be chosen on the basis of arterial supply alone.

TABLE 3. *All Amputations (1944 and 1945).*

OPERATION	NO. OF CASES		NO. OF DEATHS	
	1944	1945	1944	1945
Amputation of one or more toes	64	36	1	0
Transmetatarsal amputation	13	36	0	0
Amputation through or above mid-lower leg	37	43	2	3
Totals	114	115	3	3
Grand totals	229		6 (2.6 per cent)	

In the group of patients operated on in 1944 and 1945 it will be noted that an operation not mentioned in the previous tables is now frequently carried out (Table 3). This amputation, just proximal to the heads of the metatarsals, is made safe and practical only because virulent invasive local infection and septicemia can now be eliminated from the complications previously so serious for these

*All operations have been done by me or my former and present associates — Drs. T. C. Pratt, R. Warren, C. C. Franseen, F. W. Moore, N. J. Wilson and J. B. McKittrick.

patients (Fig. 1). The importance of penicillin in the control of infection in this group is suggested when one realizes that, in routine cultures taken from 75 patients in this group, *Staphylococcus aureus* was present in pure culture in 11 cases or in combination with other organisms (usually one of the streptococci) in 41 cases.

FIGURE 1. *Transmetatarsal Stump Nine Months after Amputation for Gangrene of the Third Toe.*
There was no dorsalis pedis pulsation, but an excellent anatomical and functional result was obtained. Note the long plantar and short dorsal flaps.

The first transmetatarsal amputation was done in March, 1944. Between then and May 1, 1946, such operations have been performed in 75 cases. Eleven of these were failures, and 1 patient died of coronary heart disease following a higher amputation. The indications for this procedure are not yet completely clear, and in certain cases a small area of necrosis on the dorsal flap (Figs. 2 and 3), which has greatly prolonged the healing time, has been disturbing. The indications for the operation will continue to be extended until a careful follow-up study of all patients satisfactorily demonstrates a clear-cut conception regarding when it should or should not be undertaken. The factors involved in the area of necrosis mentioned above are also being studied, in an attempt to eliminate this if possible. A thorough and complete follow-up examination of the late functional results in a large series of patients is also essential before the final evaluation of this procedure can be made.

This experience, however, has been sufficient to cause the conviction that amputation at this level is practical, that with the use of penicillin it is safe, that the functional result is good and that it has been and will continue to be a method that — if carefully carried out following proper preparation and under the protection of penicillin in adequate dosage — will obviate amputation at a higher level in many cases. Just how many of this group of 75 patients would have had amputation either through or above the mid-lower leg in previous years is impossible to say, but a review of the records of these patients seems to show quite clearly that at least 10 to 15 per cent, probably more, of this particular group would have had a major amputation prior to the use of this procedure.

FIGURE 2. *Areas of Necrosis on the Dorsal Flap of a Transmetatarsal Amputation for Gangrene of the Tops of the First and Second Toes of a Pulseless Foot.*
This necrosis does not involve the skin of the plantar flap and usually occurs at the site of the more lateral area.

One further improvement in technic should be mentioned. Formerly, when amputation of a digit with the head of its metatarsal was carried out for an infected joint, it was the custom to leave such a wound widely open. This large open wound required weeks, sometimes months, to heal, and in many cases the resulting scar was not good. This was especially true when the foot had been split for removal of the second, third or fourth toe with its

metatarsal head. Prior to the introduction of the sulfonamides, the practice of closing the distal portion of such wounds was begun, only the proximal third or half being left open for dependent drainage. Much to our surprise, the sutured portion of the wound healed promptly in spite of the presence of active, although well localized, infection. This "reroofing" resulted in the saving of weeks of hospital time and in marked improvement in the quality of the final scar. With penicillin, the usefulness of this procedure can be extended and the time spent in preoperative preparation can be shortened (Fig. 4).

Anesthesia

Spinal anesthesia continues to be used for all operations on the lower extremities. The injection

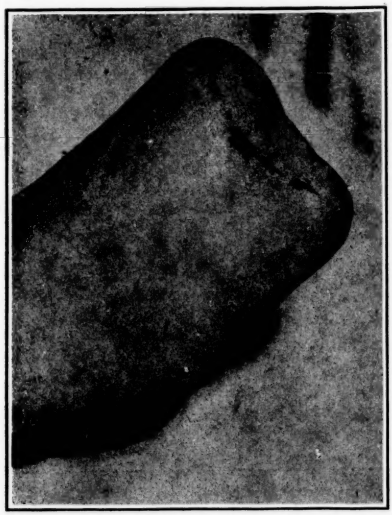

FIGURE 3. *The Same Stump Shown in Figure 2 Three Months after Revision.*

Note the excellent final result, as well as the use of a long plantar flap.

of 75 mg. of procaine crystals dissolved in spinal fluid gives excellent anesthesia of sufficient duration for any of the operations done. It is easy to use and has proved uniformly satisfactory — in fact so much so that we have found no justification for changing to the refrigeration anesthesia developed by Crossman et al.[3] and adopted by many clinics throughout the country. In this elderly group of poor-risk patients no preoperative sedation is given, since it is considered to be not only unnecessary but at times dangerous.

* * *

The importance of careful preparation of patients about to undergo elective surgery is stressed.

Marked improvement in the results of the treatment of carbuncles with penicillin is discussed.

A mortality of 4.7 per cent following major amputations for gangrene or infection of lower extremities in 212 cases is compared with a theoretical rate

FIGURE 4. *Amputation of First Toe with Its Metatarsal Head for Osteomyelitis of Metatarso-Phalangeal Joint.*

The photograph was taken three weeks after the operation. There was excellent circulation to the foot. Note the first-intention healing of the distal two thirds of the wound, which was sutured. The proximal third of the wound on the plantar surface of the foot is not well shown. The cavity was packed loosely with dry gauze at the time of operation, which was removed three days later; it was nearly healed at the time this photograph was taken.

of 5.3 per cent suggested in 1934. A mortality of 2.6 per cent following major and minor amputations in 229 cases was made possible by the discovery of penicillin.

Transmetatarsal amputations have been done in 75 cases since penicillin became available for civilian use.

205 Beacon Street

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MEDICAL EXPERIENCES WITH AMERICAN TROOPS IN THE PACIFIC*

With Remarks on the Diagnostic Value of Sternal Puncture in Malaria and on the Innocuousness of Hookworm Infection

HAROLD D. LEVINE, M.D.†

BOSTON

THIS report is based on patients seen during two years at a large United States Army general hospital in the rich Lockyer River Valley of southern Queensland, seventy miles west of Brisbane, Australia, and during a year and a half of service with another general hospital located first at Lae, on the Huon Gulf in northeastern New Guinea, and later at San Fernando, at the upper extremity of the Lingayen Gulf, Province of La Union, on the Island of Luzon, in the Philippines. Many of the observations made were new to us as individuals; others, to the best of my knowledge, are new to medicine. Alert medical officers, depending on their special interests or training, were able to make crucial observations of certain phenomena of disease, proving some ideas and disproving others. For example, one of my colleagues — a researcher on cancer in peacetime — was able to disprove the idea, long held, that betelnut chewing is carcinogenic.[1] A host of other critical observations, by-products of war experiences, will almost certainly come to light in the medical as well as in the ethnologic, anthropologic, geographic and other literature of the next few years. I am sure that many of those who have also served in the tropics could add much of interest to what I have to say about a few of the many fascinating problems met — malaria, hookworm disease, filariasis, diphtheria and scrub typhus fever.

MALARIA

When the Japanese took the East Indies they also took 90 to 95 per cent of the world's quinine. In the face of this fact and with the prospect of much tropical campaigning, the situation in the early days of the war might be described as bleak indeed. True, in the decade before the war some work had been done on the newer synthetic antimalarial drug quinacrine (Atabrine),[2] but that work had been carried out with native populations that had already developed, naturally, a partial immunity to malaria.

In the early days of the war in the Southwest Pacific the American forces followed a therapeutic antimalarial regimen that the Australians had found quite effective in the Middle East. Quinine was given for three days in doses of 0.6 gm. three times daily, followed by 0.1 gm. of quinacrine three times daily for five days and then, because of an alleged incompatibility between quinacrine and plasmochin (pamaquine), by no therapy for two days; finally, 0.01 gm. of plasmochin was given three times daily for three days. Although this schedule was modified in many ways, — for example, quinine was given in doses of 0.3 gm. three times daily during the two "free" days and concurrently with plasmochin, or this course of active therapy was followed by so-called "suppressive" quinacrine consisting of 0.2 gm. twice weekly, — the relapse rate was considerable and the number of man-days of disability from the disease was quite high. In the light of investigations begun in this country by Shannon[3] and extended in the Pacific by Bang,[3] however, utilizing the fluorescent properties of quinacrine to determine its concentration in the blood plasma, it soon became clear that the dosage necessary to attain an optimal effective level was much higher in the primary infections of nonimmune troops than that in natives seasoned to the disease. When the much heavier dosage — 0.4 gm. three times during the first day, 0.3 gm. three times on the next day, 0.1 gm. three times a day for the next four days and 0.1 gm. daily indefinitely — was used, the same prompt dramatic antipyretic response was observed that had been consistently noted with quinine. Furthermore, the impression was gained that, by and large, as much could be accomplished by the use of quinacrine alone as with added quinine or plasmochin. Finally, it was found that when the drug was continued in a dosage of 0.1 gm. daily, so that, on the average, effective suppressive levels were maintained, the relapse rate became negligible. Consequently, within a few months, instead of being a matter of great concern to the line officers and a major cause of hospitalization, cases of malaria were reported infrequently and were regarded merely as a matter of "poor Atabrine discipline" within a particular command. Before the middle of 1943, then, the malaria problem could quite definitely be said to have been whipped.

The following figures afford an idea of the splendid performance of the United States Army so far as malaria is concerned: from January, 1942, through the first seven months of 1945, there were only 207 deaths from malaria in the Army throughout the world, and of these, 20 cases were complicated by

*Read before the Belknap County Medical Society at Laconia, New Hampshire, on April 9, 1946, and before the Medical Staff of the Frisbie Memorial Hospital, Rochester, New Hampshire, on June 11, 1946.

†Assistant in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham and Beth Israel hospitals; assistant physician, Boston Dispensary.

scrub typhus fever and can therefore be excluded. I do not know how many cases of malaria developed altogether, but the figure was probably in the neighborhood of half a million. This total provides a contrast with the situation in India, where there are a million deaths from malaria every year.

The present recommended dose of quinacrine is somewhat less than that described above. In relapsing malaria it is recommended that 1 gm. be given in the first twelve hours, followed by 0.1 gm. three times daily for six days and subsequently by 0.1 gm. daily for two months. The veteran should be reassured that although he may have further relapses, the process will burn itself out in a year or two. The value of plasmochin in relapsing malaria is still in the experimental stage. There is some danger in its use, but evidence is now available that it terminates relapses from vivax malaria in a considerable proportion of cases.

During the two-year period of its operation in Australia, there were 18,693 admissions to a large general hospital. In this group there were 3358 cases of malaria — about 18 per cent of the total number. This included 2222 cases of vivax, 286 cases of falciparum and 15 cases of quartan malaria, as well as 59 of mixed types and 776 of types undetermined or unclassified.[4] Analysis of a representative sample of this material revealed many interesting facts about the symptomatology, vagaries, complications and management of malaria.[5] Among other aspects studied was the problem of so-called "chronic malaria." In contrast to the native with chronic malaria who presents the classic picture of anemia, malnutrition and asthenia, the Army patients had complaints generally falling in four groups: neurocirculatory asthenia; symptoms referable to the musculoskeletal system; vague symptoms, such as headaches, dizziness, nervousness, insomnia and tremor, referable to the central or autonomic nervous systems; and combinations of two or more of these first three groups. Essentially, these symptoms were noted in the absence of structural organic changes. Prolonged study of these men made it clear that their symptomatology rested on a psychosomatic level. When this was recognized and the patients were treated on that basis, the treatment became more effective from the standpoint of both the individual soldier and the Army. In a much more complete study of the same problem, another group of workers[6] found that maladjustment to the stresses of the illness and the difficulties of life in the combat hospital area played a major role in the incapacitation of the soldiers with malaria.

A standard teaching before the war was that there is no true causal prophylactic against malaria. Some of the work carried out during the war tended to refute this idea. In a group of so-called "provisional engineers," who went to Milne Bay in New Guinea in May and June, 1943, and who were deliberately exposed to malarial infection, a subgroup received no medication and developed malaria in 65 per cent of cases.[7, 8] In the subgroup that received quinacrine 31 per cent developed attacks of vivax malaria when the drug was discontinued. No patients in the latter group developed malaria while taking the drug during the forty-four-day period of exposure or during the voyage back to Australia, but — and this seems particularly significant — no patient, either during the period of exposure or subsequently, developed falciparum malaria. In an Australian experiment two groups of volunteers were deliberately exposed to falciparum malaria.[9] Twenty-six received suppressive quinacrine, begun twenty-two to forty-six days before exposure and continued for some time afterward. The other half served as a control and received no medication whatever. None of the former developed clinical falciparum malaria, whereas 100 per cent of the latter developed clinical falciparum malaria after the usual incubation and prepatent period. To use the words of these workers, "The absence of demonstrable parasites, the failure of subinoculation to transmit malaria, and the final demonstration of susceptibility and absence of premunity to the falciparum parasites injected into every volunteer, constituted a chain of evidence indicating that malarial infection had either been prevented by these anti-malarial drugs or cure attained."

A fortuitous circumstance led to an interesting side excursion in malarial research. Captain James R. Lyman had occasion to perform a diagnostic sternal puncture for possible kala-azar in an Australian returnee from the Middle East. The pathological report described, instead of the expected Leishman–Donovan bodies, plasmodium falciparum in the preparation. This surprising finding stimulated an investigation of the value of sternal puncture as a diagnostic procedure in cases in which several routine blood smears failed to show the parasites but in which the possibility of malaria was still strongly suspected.[10] This study was carried out during October, November and December, 1942, with Captain Lyman and Lieutenant Harold E. Young, of the Australian Military Forces, at the 112th Australian General Hospital, where large numbers of Australian soldiers, returned from the Middle East, Ceylon, Malaya and the Indonesian Islands, presented the almost routine problem of whether malaria was present, either as a single entity or in association with some other disease.

At the time this study was interrupted by our recall to our own organization, 11 such cases had been investigated. In these cases, in which thick and thin blood smears failed to show the plasmodium, it was possible to make a definite diagnosis from the bone marrow in 7 cases (Table 1). In 3 in which the bone-marrow puncture was negative (Cases 7, 9 and 10), the subsequent course of events proved that a disease other than malaria had

produced the symptoms. Another patient (Case 8) had had malaria two years previously. Twelve thick and thin smears and the examination of sternal marrow were negative, yet quinine produced a prompt and convincing drop in the temperature. It is therefore obvious that although sternal puncture may bring to light some cases of malaria, it is not infallibly positive in the presence of malarial infection. No attempt was made to compare the value of this method with that of other methods of detecting obscure cases of malaria, such as the complement-fixation test and examination of the blood smear following epinephrine injection. It is fair to state that subsequent improvement in the accuracy of routine laboratory blood examinations for the malarial plasmodia dampened our interest in sternal puncture. Examination of the literature on our return to this country, however, showed a similar enthusiasm for the method before[11–13] and since[14–16] the onset of the war. Sternal puncture may be regarded as an expedient, safe and rapid method of investigating malaria that may be positive when repeated thick and thin blood smears fail to show the parasites. The method seems to deserve more extensive investigation in the future.

TABLE 1. *The Results of Sternal Puncture in the Diagnosis of Malaria.*

CASE NO.	DIAGNOSIS	NO. OF NEGATIVE BLOOD SMEARS	RESULTS OF STERNAL PUNCTURE
1	Benign tertian malaria; bleeding duodenal ulcer	6	+
2	Benign tertian malaria	2	+
3	Benign tertian malaria	1	+
4	Benign tertian malaria	4	+
5	Malignant tertian malaria; kala-azar	4	+
6	Benign tertian malaria	1	+
7	Septicemia	4	—
8	Chronic malaria	12	—
9	Chronic malaria ?	4	—
10	Amebic dysentery	3	—
11	Benign tertian malaria	3	+

HOOKWORM INFECTION

In the wake of the Papuan campaign there was, for a time, much preoccupation with the symptomless ovum passer and the attempt to render his stools free of hookworm ova. But the distinction between hookworm disease and hookworm infection and the over-all innocuousness of this infection in our troops were soon appreciated, and the condition dealt with more rationally. Some time later I analyzed a limited series of 70 patients at a general hospital in northeastern British New Guinea.

The symptomatology in this series could be divided into three general groups, the first of which comprised 43 patients with a multiplicity of symptoms, such as nervousness, tremor, apprehension, insomnia, nightmares, battle dreams, somnambulism, headache, dizziness, lethargy, depression, anxiety, temper outbursts, emotional instability and precordial pain. Dyspeptic symptoms were also noted by 14 patients, but in 2 of these they were specifically related to combat and in 2 others they antedated military service. Of 34 patients treated and followed, 29 were successfully dewormed and 5 were not. Only 2 of those who were successfully dewormed were rendered free of symptoms. All the others, whether dewormed or not, continued to have the same complaints.

The second group consisted of 19 patients in the active or convalescent stage of a well defined disease with symptoms limited to those characteristic of that condition; the finding of hookworm infection was merely incidental. This group included 3 cases of infectious hepatitis, 2 of scrub typhus (tsutsugamushi) fever in the convalescent stage, 7 of various skin diseases, 2 of bronchial asthma and 1 each of bacillary dysentery, rheumatoid arthritis, urethritis, migraine and malaria. The subsequent course was typical of the particular disease presented.

The third group included 8 patients whose symptomatology was limited to the gastrointestinal tract. The symptoms comprised postprandial epigastric pain or cramping, periumbilical discomfort, a heavy sensation in the abdomen, gaseous distention and burning sensations in the stomach. Three of these patients were dewormed, and 5 were not. Unfortunately, in most cases in this study, worm burden or ova counts were not made, so that the possible effect of treatment in decreasing the worm burden cannot be stated. Nevertheless, in all cases, the symptoms either were greatly alleviated or disappeared entirely. It must be stated, however, that most of the patients were aware of the diagnosis, and it is possible that the psychotherapeutic effect of a definite treatment for a definite disease contributed to the successful outcome.

In the entire group the hemoglobin as determined by the Sahli method ranged from 11.8 to 14.8 gm., with a mean of 13.3 gm. In all but 4 cases the determinations exceeded 12.4 gm. The red-cell count ranged from 3,840,000 to 5,400,000, with a mean of 4,540,000. In only 1 case did the determination fall below 4,150,000. In view of the fact that, from a history of exposure, these patients had had the hookworm infection for from three to thirty months, it seems unlikely that, subsisting on the regular army diet, American troops developed any significant anemia from hookworm.

This observation of lack of anemia is in agreement with the observations of Rhoads et al.,[17] who found that, in the presence of an adequate iron balance, anemia does not develop in patients with hookworm infection. In the present study, moreover, it appeared that the only soldiers with hookworm infection in whom treatment was helpful were the small group with purely dyspeptic symptoms. Furthermore, it is generally accepted that in the

absence of reinfection the hookworm eventually dies. The period of parasitism has been regarded as from a few months to several years. It is apparent, then, that from the immediate and long-run point of view, hookworm infection was largely innocuous in American soldiers. Hence the wise and expedient policy eventually formulated of treating ovum passers arbitrarily, of not following the effects of treatment unless the patient was to remain in the hospital for other reasons and of discharging him to duty possibly to have further stool examinations and treatment at a regimental dispensary. In the rare patient with a heavy infection, on the other hand, thorough treatment and adequate follow-up study were necessary.

Miscellaneous Diseases

Filariasis

A large number of soldiers were seen at the hospital in the summer of 1943 because of the probability of early filariasis. This group had been on Tongatabu, an island of the Samoan group, for exactly a year. Their symptoms were lymphadenitis,[18] with fugitive dome-shaped swellings of the arms and legs, retrograde lymphangitis, varicocele, orchitis, epididymitis and recurrent funiculitis, the spermatic cord becoming enlarged, either spontaneously or after a deliberate exercise test,[19] to several times its normal diameter. In all but 1 case in this entire group, repeated day and night smears failed to reveal the presence of microfilaria. Much more helpful diagnostic aids were the clinical course in soldiers who had been in endemic areas, an intelligently interpreted intradermal test and lymph-node biopsy with the finding of adult filarial worms or a characteristic tissue reaction. These men — familiar with the sight of native Tongans with advanced elephantiasis, envisaging a future behind a wheelbarrow full of scrotum and fearful of sterility in later life — were an extremely unhappy and apprehensive lot. Credit is due Major Paul Kunkel for the understanding and sympathetic way in which this group of soldiers was handled. The patients were told that in the absence of reinfection the likelihood of permanent changes was nil; this reassurance was vindicated by the subsequent course of events, as observed at special convalescent hospitals and elsewhere.[20, 21]

Diphtheria

It was rather a surprise to learn that diphtheria is an important and widely prevalent tropical disease. Many cases of cutaneous and several of pharyngeal and nasal diphtheria were observed, as well as a few with residual peripheral-nerve palsies and one dying with, if not of, myocarditis. In a thoroughgoing investigation of this disease at Lae in British New Guinea, Cutts[22] found that it was indeed the dermatologic wards that served as a constant reservoir of this infection. Cultures from the skin of many patients with a wide variety of skin diseases showed virulent diphtheria bacilli. The lesions of skin diphtheria seen at this hospital were almost uniformly rather sharply defined, blackish to brownish-black, ulcerated areas with indurated bases,[23] yielding virulent diphtheria bacilli on culture, and located in traumatized areas about the heel or between the toes, where they were spindle shaped, and giving a suggestive if not characteristic appearance. Cutaneous diphtheria must constantly be thought of in the tropics or the diagnosis is apt to be missed.

During this overseas experience a large number of patients were seen with peripheral neuritides, some isolated, some multiple, some involving the scapulohumeral group and producing the so-called "winged scapula" or involving the peroneal or other groups and some without and some with an elevation of the spinal-fluid protein in association with a normal or only slightly elevated cell count, producing the Guillain–Barré syndrome. In many of these cases early failure of the muscles of accommodation of the eye was suggested by the history or demonstrated by examination. Evidence accumulated during the course of the war became more and more conclusive that these neuritides were the residua of previous diphtheria, usually unrecognized.[24] If one is consulted by a veteran complaining of having developed "infantile paralysis" or some obscure neuritis during his tropical experience, it may be helpful to bear this point in mind.

Scrub Typhus Fever

This disease, with a mortality of from 2 to 30 per cent (average, 5 per cent), was far more serious than any other mentioned so far. It is caused by a rickettsia similar to those of epidemic and endemic typhus fever and of Rocky Mountain spotted fever. Its reservoir in New Guinea consists of certain field rats or voles or bandicoots, and its vector is a larval mite that clings, among other sites, to the lower portion of the stalk of the kunai grass, which is abundant on this island. The disease principally affected troops campaigning in uncleared areas. The acute illness is characterized by an eschar developing in a few days after the bite, with marked regional and less marked generalized lymphadenopathy, chills, a high fever, a rash, the development of agglutinins against the Kingsbury strain of Proteus bacillus, cough, prostration, deafness, palsies and certain mental symptoms, such as headache, lethargy, delirium and coma. The disease generally runs a remittent course for two weeks, with evidence of pneumonitis and involvement of the cardiovascular system (tachycardia, hypotension, cardiac irregularities and gallop rhythm) supervening during the second week. All grades of severity were encountered, death generally occurring late in the second week. The most prominent post-mortem changes were a generalized

vasculitis and perivasculitis, with lymphocytic and plasma-cell exudation and with a predilection for the lungs, where an interstitial pneumonitis and hemorrhagic edema was produced, for the brain, where focal parenchymatous lesions referred to as "typhus nodules" eventually appeared, and for the heart, where the disease resulted in varying grades of diffuse interstitial or focal perivascular infiltrations of the same cellular types, as well as varying degrees of heart-muscle necrosis. Although there is no question that myocardial damage is present in the acute phase of the disease, the question whether these patients die in acute congestive heart failure is still debated.[25] Many of the survivors of this disease were debilitated for months and required prolonged periods of reconditioning before they could return to duty. Clinical[26] and pathological[25] studies following recovery showed no evidence of persistent myocardial damage and seem to indicate that much of the disability resides in the peripheral vascular system rather than in the heart.

Amebiasis

It should not be forgotten that many patients who have had amebic dysentery will continue to have diarrhea, presumably as a result of residual scarring of the bowel, even after the organism has been eliminated. In any patient with a history of amebic dysentery while in the service it is therefore essential to carry out a sigmoidoscopic examination and, if ulcers are present, to obtain swabbings or washings from the ulcers and to search for the organism. This may prevent the physician from initiating futile treatment. It is also well to remember that some of the drugs used in the treatment of amebiasis, such as chiniofon, are in themselves capable of inducing diarrhea.

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To a civilian, the yellowed, underweight soldier returning from the tropics with a story of rigorous privation, starvation, extreme intolerable heat and disease conjures up an appalling picture of the "dank, steaming" malaria-ridden tropics. And yet the same civilian is amazed at the improvement in this soldier a month or two later, when he has excreted the quinacrine that was merely staining his tissues and when he has regained the weight lost as a normal physiologic reaction to the tropics. Is it possible, one might ask, that the soldier has failed to differentiate the unpleasant effects of field, combat or garrison conditions, with their attendant fatigue and boredom, from those due to the tropics per se? Many of the officers and enlisted men I questio ed on this point admitted that life there in peace ime, with their families and with the conveniences and recreations and diet of the civilian, would not be unpleasant.

Interestingly enough, in spite of the high temperatures and humidities, no genuine cases of heat stroke or heat exhaustion were observed during this service in New Guinea, Luzon and in semitropical Australia, presumably owing to an adequate process of acclimatization in the troops. Nor did the occasional elevations of temperature that had been expected on extremely hot days occur. In fact, many of my associates agreed that the days were much more comfortable than the so-called "dog days" of July or August in Washington or even in Boston.

Summary

Medical experience in the Pacific in World War II has extended the knowledge of certain tropical diseases. Among other observations the following are noteworthy.

Quinacrine (Atabrine), at first regarded as a makeshift substitute for quinine, was found to be a more effective therapeutic and suppressive agent than the latter against malaria and eventually made that disease a relatively unimportant military problem.

So-called "chronic malaria" as it existed in American troops differed from the classic picture: instead of anemia, malnutrition and asthenia, the troops presented various psychosomatic patterns largely without demonstrable organic disease.

Sternal puncture may reveal malarial plasmodia when repeated thick and thin blood smears fail to show the organism. In experienced hands, however, repeated thick and thin smears are satisfactory in the vast majority of cases.

Hookworm infection is to be distinguished from the hookworm disease. Parasitism is largely innocuous in American troops. Only parasitized troops with purely dyspeptic symptoms may expect relief from their symptoms after treatment.

Day and night blood smears are almost invariably negative in early filariasis. Lymph-node biopsy, the typical clinical course and skin tests, intelligently interpreted, are much more helpful in arriving at the diagnosis. Although fear of chronic invalidism was prominent in the minds of infected soldiers, evidence at hand indicates that permanent residua are unlikely.

Cutaneous diphtheria and, to a lesser extent, nasal and pharyngeal diphtheria are important tropical diseases. The dermatologic wards form a constant reservoir for the organism. Many cases of unrecognized diphtheria are followed by obscure neuritides, some with a Guillain–Barré type of spinal-fluid pattern.

Scrub typhus (tsutsugamushi) fever may produce severe fatal lesions of the heart, lungs or brain. There is neither clinical nor pathologic evidence of persistent heart disease following the infection.

171 Bay State Road

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MEDICAL PROGRESS

DIGITALIS*

A. S. Freedberg, M.D.,† and Paul M. Zoll, M.D.‡

BOSTON

In recent years many reports have appeared on new purified digitalis preparations. Revisions have also been made in the *U.S.P.* unit of potency of digitalis, with changes in the method of assay as well as in the strength of the official preparation. Many cases of severe toxicity from digitalis have recently been reported[1-5] that indicate considerable confusion regarding the choice and dose of digitalis substances. It is the purpose of this paper to discuss the present status of whole-leaf digitalis and several purified digitalis bodies.

Assay

In the twelfth revision (1942) of the *United States Pharmacopoeia* the cat method of assay was employed for the first time. One cat unit is defined as the amount of digitalis per kilogram of cat weight that produces a lethal effect under certain defined conditions. One *U.S.P. XII* unit of digitalis represents the same potency as 0.1 gm. of the *U.S.P.* digitalis reference standard powder, when assayed as directed. The digitalis leaves from which the reference powder was made, however, were of high potency, so that 1 *U.S.P. XII* unit is equivalent to 20 per cent more than 1 cat unit. It is particularly important for the physician to know the digitalis preparation he is using, since the clinical effect of digitalis, standardized according to *U.S.P. XII*, is approximately 25 per cent weaker than *U.S.P. XI*, which in turn is approximately 50 per cent stronger than *U.S.P. X*.

The latest revision has led to more uniform preparations but has not solved the difficulties of assay. There are many variables inherent in the technic of assay by the cat method, such as the rate of injection,[6,7] body temperature of the animal[8] and depth and type of anesthesia. The increased toxicity of digitalis observed in cats with elevated body temperatures may be of clinical significance in explaining the deleterious effect of digitalis in patients with febrile illnesses. Further objections may be raised that the cat method of assay measures the lethal potency of digitalis and not specific therapeutic action.[9-15] Bio-assays by other methods[15-17] offer no advantages over the standardized cat procedure.

A chemical assay based on the presence of an active hydrogen atom in the unsaturated lactone group in digitalis has been developed.[18] Further studies have shown, however, that the proposed chemical method does not measure total biologic activity[19] and does not yield consistent results.[20]

Human Method

Since the cat method of assay involves intravenous injection of digitalis substances, differences in absorption of the drugs from the gastrointestinal tract are not taken into account. Completely nonabsorbable fractions may have significant potency according to the cat method of assay.[21] Gold[22]

*From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School. Aided by a grant from the Life Insurance Medical Research Fund.

†Instructor in medicine, Harvard Medical School; associate visiting physician and associate in medical research, Beth Israel Hospital.

‡Assistant in medicine, Harvard Medical School; associate in medicine and associate in medical research, Beth Israel Hospital.

showed the error in translating potency of digitalis from cat units to clinical potency in man; by comparative assays in cats and human beings, a group of digitalis preparations with the same strength in cat units showed a tenfold range in potency in human subjects.

The assay of digitalis preparations in human subjects has been developed by measuring the effect on the electrocardiogram. Bromer and Blumgart,[23] using the three standard leads, found that changes in the T wave of the electrocardiogram could be used as a quantitative index of the amount of digitalis effective within the body. In other studies,[24, 25] which failed to demonstrate a quantitative correlation between the amount of the drug and the resultant electrocardiographic effects, only Lead 2 was recorded.[24, 25] Although effects with digitalis were inconstant in the standard leads, Goldberger[26] noted the constant production of changes in the T waves and the ST segments in unipolar limb leads. More recently the quantitative effects of a digitalis substance on the electrocardiogram were measured by the analysis of the ventricular gradient.[27] This method is not yet suitable for human assay of digitalis.

Satisfactory assays in normal human subjects have been accomplished by Gold,[28, 29] who produced qualitatively similar effects on the T wave and the ST segment with known and unknown preparations of digitalis. After control tracings (Leads 1 and 2) a dose of digitalis was given and the electrocardiogram repeated in twenty-four hours. In four experiments on the same subject, the electrocardiographic changes induced by doses of 100 per cent, 122 per cent and 149 per cent of a standard preparation of digitalis were compared with those following the digitalis substances to be assayed. The unknown preparations of digitalis were thereby assayed in human beings with an error of 25 per cent. Geiger et al.,[30] on the other hand, concluded that progressive digitalization produced electrocardiographic changes that were too small and inconstant to yield any quantitative correlation. A review of their actual data reveals, however, that in 3 of 10 normal subjects progressive digitalization caused increasing changes in the T waves. It was through the use of a few selected subjects like these that Gold was able to assay digitalis in human beings.

It is clear that such an assay is desirable because of the closer parallelism with clinical experience. Although the method proposed by Gold is the best available at present, its results have not yet been confirmed; it requires time, and relatively few subjects are suitable for assay. Furthermore, since the estimation of the electrocardiographic effect of digitalis depends on the judgment of the electrocardiographer regarding when equivalent changes in the T wave are produced, other causes of T-wave changes must be excluded. These include spontaneous variations and those induced by changes in heart rate, as well as by food, drink, exercise, excitement, infections and fever, position and hyperventilation.[31–36]

Cardiodynamic Effects

Since the assay of digitalis by the cat method is still imperfect and does not exactly reflect the clinical potency of the drug, the physician's skill is of paramount importance in the therapeutic use of digitalis. The rational use of digitalis demands understanding of its effects on the cardiovascular dynamics in congestive heart failure in human subjects.

It is almost universally agreed that administration of whole-leaf digitalis and purified glycosides in patients with congestive heart failure results in an increased cardiac output or a decrease in arteriovenous oxygen difference,[37–49] lowered venous pressure[14, 40, 43, 46, 47, 50–54] a faster circulation time[14, 40, 47, 53, 54] and a diminished blood volume.[55, 56] The fall in venous pressure may precede diuresis and slowing of the pulse rate.[43, 51, 52, 54] Recently, Stewart et al.[14] reported an increase in peripheral circulation as a whole after digitalization. The increase in cardiac output is obtained without a proportionate increase in cardiac work or oxygen consumption. The failure of cardiac output to return completely to normal after digitalis[51] confirms the clinical evidence that most patients with congestive failure require additional therapy, such as limitation of activity, salt restriction and diuretics.

After digitalization the vital capacity is increased,[46, 47] the respiratory minute volume is reduced[38, 47, 57] and the alveolar carbon dioxide content is increased.[44] The basal metabolic rate falls.[14, 44] Digitalization results in a decreased oxygen debt after exercise.[58]

In patients with auricular fibrillation and a rapid ventricular rate digitalis induces significant slowing of the pulse rate. This effect has a twofold origin: vagal stimulation by therapeutic[59, 60] or subtherapeutic[61, 62] doses, which may be obliterated by atropine or exercise; and a direct action on the nodal tissues and myocardium, which cannot be obliterated thereby.

Considerable controversy exists concerning the exact mechanisms of the action of digitalis. According to some observers the therapeutic effect of digitalis is extracardiac in origin. Dock and Tainter[63, 64] proposed another mechanism of action of digitalis — hepatic-vein constriction, with consequent reduction in venous return and in right auricular venous pressure, an effect comparable to venesection. Among other objections to this hypothesis is evidence that this mechanism does not obtain in human subjects.[65, 66] The effects on vagal activity and the conducting tissues of the heart mentioned above do not account entirely for the beneficial response, which may occur without or before a change in rate. A large body of physiologic[67–69] and electrocardiographic[27, 70] data indicates a direct action of digi-

talis on heart muscle. In this connection, Guttman[71] has demonstrated the chemical union between digitoxin and striated muscle; such a combination with heart muscle has not yet been reported.

Whole-Leaf Digitalis

Indications

In the light of the cardiodynamic effects of digitalis, it may be stated that the primary indication for the clinical use of digitalis is congestive heart failure. Sufficient data are available to indicate the beneficial action of digitalis in congestive failure irrespective of the etiology of the disease or the type of cardiac rhythm.[4, 72–80] Additional indications include auricular flutter, persistent auricular fibrillation and heart disease associated with hypertension or valvular disease to prevent cardiac hypertrophy and congestive failure.[81–83]

Digitalis substances have been used successfully in the treatment and prevention of episodes of paroxysmal auricular tachycardia and paroxysmal auricular fibrillation.[80, 84–87] Although it has been assumed that the beneficial action in auricular arrhythmias is related to vagal stimulation, the mechanism of the action has not been established.[88] The changes in cardiovascular dynamics that occur with constrictive pericarditis in the absence of auricular fibrillation, thyrotoxicosis, infection, shock and anemia are not indications for the use of digitalis.

Contraindications

It should be stressed that there are no absolute contraindications to the use of digitalis in the presence of congestive heart failure. In the absence of congestive failure contraindications include multiple ventricular extrasystoles and ventricular tachycardia, angina pectoris[89, 90] or myocardial infarction,[89, 91] recent or old, hypersensitivity of the carotid sinus,[92] Stokes–Adams syndrome and partial heart block.[93] Blumgart and Altschule,[94] however, showed that the administration of therapeutic amounts of whole-leaf digitalis to patients with partial heart block was not followed by an increase in the block.

The effect of digitalis on intravascular clotting has recently been the subject of considerable investigation. It has not yet been established that digitalis significantly alters the blood coagulation time.[95–100] It has been suggested that digitalis is a factor in the formation of fatal emboli by its thromboplastic effect or by the mobilization of endocardial thrombi.[91, 101, 102] The clinical data presented are not decisive.

Clinical Use

Many schedules have been devised for the administration of digitalis.[80, 103–105] It must be remembered that routine administration strictly according to a preconceived plan is not advisable because of variations in the drug and in the patient. In most cases of congestive heart failure in which the drug has not been previously administered, digitalization may be accomplished by giving 0.3 gm. of digitalis purpurea (*U.S.P. XII*) three times the first day and 0.1 gm. three times daily thereafter until the optimal therapeutic effect or symptoms of minor toxicity appear. Such a scheme avoids excessive delay in therapeutic result and also minimizes the risk of undesirable toxic manifestations. In patients with auricular fibrillation and a rapid ventricular rate, slowing of the ventricular rate approximately to 70 is a satisfactory end point. In patients with normal rhythm or with auricular fibrillation and slow ventricular rate, evidence of satisfactory digitalization consists of marked clinical improvement or the appearance of early toxic manifestations, such as anorexia and extrasystoles. When a clear end point is reached, the drug may be discontinued for a day, if necessary, and a daily maintenance dose of 0.1 to 0.2 gm. administered.

A reliable preparation of whole-leaf digitalis should be used with which the physician is familiar; changing from one preparation to another is undesirable. In the few cases in which whole-leaf digitalis is not tolerated or more rapid digitalization is needed, a purified glycoside is preferable, either in a single oral dose or intravenously. Recently, many purified preparations of digitalis bodies have been offered to the physician. These are crystalline, do not require biologic assay and can be prescribed in terms of weight of the drug.

Strophanthins

Ouabain is obtained in pure crystalline form from *Acocanthera ouabaio* and *Strophanthus gratus*. From *Strophanthus kombé* is obtained K-strophanthin, an amorphous mixture of glycosides. K-strophanthin-alpha (Cymarin), K-strophanthin-beta and K-strophanthoside are pure crystalline glycosides that have been isolated from this mixture. The absorption of all these substances from the gastrointestinal tract is so irregular and poor that they are not suitable for oral use.[106, 107] Recently, Gold et al.[108] studied a series of synthetic esters of the aglycone strophanthidin, one of which — the benzoate ester — was somewhat effective orally.

Although the strophanthins induce the same qualitative physiologic effects after intravenous injection as digitalis, quantitative differences exist. They are the most rapidly acting glycosides, inducing a decrease in ventricular rate and venous pressure in the first three or four minutes after administration,[51] with a maximum effect in thirty[52] to one hundred and twenty minutes[22] and a total duration of effect from twenty-four to seventy-two hours.[109, 110]

Clinical Use

It has been recommended that K-strophanthin or ouabain be given intravenously in doses of 0.3 to

0.5 mg. for immediate digitalization[80, 84, 104, 109–112]; 0.1 mg. may be administered every half hour to hour thereafter until full digitalization is accomplished. The short duration of action raises the problem of subsequent maintenance of digitalization. For this purpose, it has been recommended that, together with 0.5 mg. of ouabain intravenously, whole-leaf digitalis be given orally — 4 cat units to patients weighing less than 125 pounds, 6 to patients weighing 125 to 175 pounds, and 8 to patients weighing more than 175 pounds.[53, 109, 110] At the end of twenty-four hours the patient may be placed on a daily maintenance dose of whole-leaf digitalis.

The only advantage possessed by the strophanthins over other purified glycosides is the rapid onset of action. Many considerations, however, make them unacceptable to the physician. Their stability in solution has been questioned.[109] They are irritating when deposited extravenously. Finally, maintenance of digitalization is difficult as a result of the short duration of action. Combinations with whole-leaf digitalis or other slowly acting drugs are difficult and unsatisfactory for routine use in that they often lead to toxicity or lack of adequate digitalization. In the relatively few emergencies in the treatment of congestive heart failure or paroxysmal arrhythmias, therefore, the physician uses to better advantage one of the other more stable, less irritating, purified glycosides with rapid and prolonged action.

Lanatoside C

Lanatoside C (digilanid C or Cedilanid) is the only one of the three lanatosides occurring in *Digitalis lanata* that is not present in *Dig. purpurea*. Many studies stimulated by the work of Moe and Visscher[9, 10] have been made comparing the potency, absorption from the gastrointestinal tract, speed of action and elimination, type of cardiac effect, therapeutic to toxic ratio, toxic effect and clinical effectiveness of lanatoside C with those of other preparations.

Absorption and Potency

Although the absorption of lanatoside C in animals[113] is much faster and more complete than that of whole-leaf digitalis, studies in human subjects have yielded conflicting results.[114–116] The intravenous digitalizing dose in man of lanatoside C is agreed to be 6 cat units (1.6 mg.), somewhat more than the oral and intravenous digitalizing dose of 3 cat units (1.2 mg.) for digitoxin.[22, 85, 116] The single oral digitalizing dose for lanatoside C varied from 5 to 10 mg.[22, 114, 117] The threefold to sixfold increase in oral over intravenous dose is due presumably to poor and variable absorption of the drug. It must be concluded that the absorption of lanatoside C is much less complete and more variable than that of digitoxin.

Time of Action

Accurate information is available regarding the relative speed and duration of action of lanatoside C. Following intravenous injection, the earliest effects were noted in ten to thirty minutes. This onset of action was measured by the fall in venous pressure,[40, 51, 52, 68, 69] slowing of ventricular rate,[51, 52, 70] increased cardiac output,[40, 68, 69] diminution in diastolic heart volume or oxygen consumption,[40, 68, 69, 118] and electrocardiographic changes.[24, 70] The effect is maximal in approximately two hours,[70] persists sixteen[24] to thirty-six hours[70] and disappears in three to six days.[70] In comparison with that of other glycosides, the onset of action of lanatoside C is slower than that of ouabain, similar to that of digoxin and considerably faster than that of digitoxin; the duration of effect is longer than that of ouabain and digoxin but considerably shorter than that of digitoxin.

Toxicity

No differences were found in the production of myocardial cellular damage[119–121] and associated electrocardiographic changes[122, 123] by toxic doses of various glycosides, including lanatoside C. Kyser et al.[121] related the probable mechanism to vagal stimulation and coronary constriction, since the lesions could be prevented by atropine or purines given at the same time as the digitalis drugs.

The prolonged intravenous administration of lanatoside C to dogs in small doses for over a year produced no harmful effect on the myocardium.[120] As with other glycosides, it does not reduce coronary blood flow at therapeutic or subtoxic levels.[124, 125]

In its ratio of minimal therapeutic to toxic dose, lanatoside C ranked next to ouabain and far above lanatosides A and B.[9, 10] Cattell and Gold,[15] however, were able to demonstrate no difference in the ratio of therapeutic to toxic dose of a large number of cardiac glycosides, including lanatoside C. Nevertheless, many effects that contribute to the total toxic action of digitalis bodies cannot be observed in the experimental method employed.

Clinical Use

For intravenous digitalization 1.2 to 1.6 mg. may be followed by subsequent administration of 0.4 mg. at intervals of four to eight hours until the full digitalizing effect is noted. In this way, complete digitalization is rapidly reached and danger of toxicity reduced in spite of individual variations in susceptibility to the drug. Although 7.5 to 10.0 mg. in two or three days is recommended in most studies for oral digitalization with lanatoside C, it has already been noted that there is a wide range in the required dosage. The broad range in the daily maintenance dose, from 0.5 to 3.0 mg., indicates the difficulty in maintenance of digitalization. This may be due to the rapid elimination and poor absorption of lanatoside C.

Particular stress has been placed on the value of digitalis, particularly intravenous lanatoside C, for its rapid action in arrhythmias, such as paroxysmal auricular tachycardia, auricular flutter and auricular fibrillation, and even in chronic auricular flutter and fibrillation.[24, 80, 85, 87] Full digitalization was accomplished at the onset of the paroxysm and maintained by the daily use of 0.5 to 1.0 mg. over long periods. Although this schedule reduced the incidence of paroxysms, there is no evidence that lanatoside C accomplishes more than other digitalis preparations in the treatment of auricular disorders.

In summary, lanatoside C is a potent glycoside with all the actions of digitalis preparations. The advantages claimed, such as a greater margin of safety, greater cardiac efficiency and lack of reduction of coronary blood flow, are not yet proved in clinical practice. It is rapidly although poorly absorbed from the gastrointestinal tract. The relatively rapid excretion of lanatoside C, although perhaps a factor of safety in reducing the incidence and duration of toxic manifestations, is also a disadvantage, since maintenance of digitalization is difficult. The rapidity of effect on intravenous administration makes lanatoside C preferable to digitoxin in the relatively few acute emergencies in which the time differential may be important.

Digoxin

Digoxin, a purified glycoside isolated from lanatoside C by hydrolysis, is apparently the active cardiac principle in lanatoside C. Its physiologic effects on the heart and its toxic manifestations are similar qualitatively to those of the other digitalis bodies.[25, 43, 51, 52, 70, 126, 127] Quantitative differences in the rate and extent of absorption from the gastrointestinal tract, as well as in the rate of elimination, differentiate digoxin from the others in clinical application.

Time of Action

Digoxin is similar to lanatoside C in its speed and duration of action; its effects become apparent in three to thirty minutes, are maximal in approximately one and a half to five hours and regress as early as eight to ten hours, being largely gone in twenty-four to thirty-six hours and completely absent in two to six days. These actions are appreciably more rapid than those of digitoxin. Batterman and DeGraff[128] clearly demonstrated the relatively rapid rate of elimination of digoxin. They digitalized 38 patients to the point of minor toxicity by giving 0.5 to 1.0 mg. of digoxin every six hours. After varying intervals, they repeated the administration with the same schedule to the same level of toxicity. The fraction of the initial dose necessary to reproduce the same level of toxicity after intervals of twenty-four, forty-eight and seventy-two hours was 49, 84 and 87 per cent respectively. These percentages indicate the amounts of the drug lost in the intervals of time. The rapid elimination of the drug was further demonstrated in that, when an adequate single daily maintenance dose was given in divided portions, it became obviously insufficient, with resultant reappearance of congestive failure. This study is particularly cogent since a clear-cut, readily reproducible end point — namely, minor toxicity — was used, so that the same level of digitalization was clearly obtained even under conditions of clinical study. The usual objections to so many clinical investigations were avoided in that undefined levels of "full digitalization," "desired cardiac effects" and "improvement in congestive failure" were not used.

Clinical Use

Many studies have clarified the clinical effectiveness of digoxin.[54, 78, 80, 104, 126, 127, 129, 130] The average therapeutic and toxic doses on rapid oral administration were 3.75 and 6.0 mg. respectively; 1.0 to 2.0 mg. may be given initially, followed by 0.5 mg. every six hours until the desired effects are produced.[104] For intravenous digitalization 1.0 mg. may be injected, followed by 0.5 mg. every six hours as necessary. The oral maintenance dose varied from 0.25 to 1.25 mg. daily. In some cases as much as 1.0 mg. three times daily was necessary for maintenance of digitalization.[104]

In summary, digoxin is a potent substance that is valuable for rapid digitalization, with no particular advantage over lanatoside C. Its relative insolubility and irritating character make intravenous administration difficult. The difficulty of maintaining full digitalization over the long periods necessary in chronic congestive heart failure is a serious disadvantage.

Digitoxin

Digitoxin, or *digitaline crystallisée*, was isolated by Nativelle[131, 132] in 1866 and was proved to be a potent cardiac drug by Vulpian.[121] In 1875 Schmiedeberg[133] isolated a crystalline substance from digitalis leaves, which he named digitoxin, and stated that it formed the bulk of *digitaline crystallisée*. Although some data[106, 134, 135] indicate that preparations of *digitaline crystallisée* and digitoxin differ in potency, the *United States Pharmacopoeia* treats them as if they were the same.

Pharmacology

Digitoxin is completely absorbed from the gastrointestinal tract in animals and human beings. Thus, the intravenous and oral doses are the same.[136] If the oral absorption of digitoxin is judged by the decline in ventricular rate, it is complete in four to ten hours.[136, 137] On intravenous injection the initial effects were noted in twenty-five minutes to two hours, with maximal effects in two to nine hours. Regression of effect began in two or three days, the total duration of action lasting approximately two weeks.[51, 67, 70, 134]

The potency of 1 mg. of digitoxin is approximately equal to 1000 mg. of *U.S.P. XII* digitalis reference powder. Thus, 1.25 mg. of digitoxin induces the same degree of reduction of ventricular rate as 1.25 gm., or 16.3 cat units, of whole-leaf digitalis. The cumulative action of digitoxin is similar to that of whole-leaf digitalis; in patients with auricular fibrillation, the administration of small daily doses — 0.2 mg. — resulted in a gradual decline of ventricular rate to normal levels in about three weeks.[134, 138] Maintenance of this dosage during a subsequent prolonged period induced no further change of rate. It may therefore be concluded that the excretion of digitoxin, like that of whole-leaf digitalis, is a function of the amount available within the body rather than the amount administered. Gold et al.[138] found no significant difference in the ratio between the toxic and therapeutic dose for digitoxin as compared to digitalis.

Toxicity

The toxic actions of digitoxin were first observed by Koppe,[139] who took 3.5 mg. in five days, suffering severe toxic symptoms, nausea and vomiting, a slowing of the pulse rate from 80 to 40 and a bigeminal rhythm that became grossly irregular. Gold[67, 137] noted that a single oral digitalizing dose of digitoxin of 1.26 mg., or 3 cat units, induced nausea within two hours in only 2 per cent of a large series of patients. This was presumably due to the local gastric emetic action of digitoxin. An equivalent dose of whole-leaf digitalis produced early nausea in 20 per cent of the same group. With a single dose of 2 mg. of digitoxin, 32 per cent of the patients developed minor toxic symptoms, and 20 per cent vomited. There seems to be ample evidence that digitoxin induces the same incidence of late or central toxicity as whole-leaf digitalis.[140, 141] Toxic doses of digitoxin, as with other glycosides, administered to animals are associated with the development of myocardial lesions,[119, 121] changes in the ST and T waves[122, 123] and a reduction in coronary blood flow.[125]

Clinical Use

Stroud and VanderVeer[130] observed that the digitalizing dose of digitoxin was 1.3 to 2.2 mg. when given orally over a period of three to six days. The maintenance dose was 0.1 mg. daily. In many hundreds of patients with auricular fibrillation and a rapid ventricular rate Gold et al.[134, 138] found that a single oral or intravenous dose of 1.2 mg. carried the process of digitalization fairly far.[134] They recommended subsequent daily doses of 0.2 mg. to complete and maintain full digitalization. It must be remembered that full digitalization cannot be achieved promptly by this routine in all cases.[29, 135, 141] In undigitalized patients, a single dose of 1.2 mg. may be given by oral or intravenous route. The subsequent administration of digitoxin to achieve full digitalization depends for its end point on whether the patient has auricular fibrillation with a rapid ventricular rate, auricular fibrillation with a slow ventricular rate or normal rhythm. In the presence of auricular fibrillation with a rapid ventricular rate, 0.2 to 0.4 mg. should be administered at intervals of six to eight hours until the ventricular rate reaches approximately 70; it is not necessary to carry such patients to the point of minor toxicity. To complete full digitalization in patients with auricular fibrillation and a slow ventricular rate or with normal rhythm, additional digitoxin, in a dose of 0.2 to 0.4 mg., must be administered at intervals of six to eight hours until the earliest toxic symptoms are produced. It must be kept in mind that the desired clinical response may occur as a result of partial digitalization. In our experience, the subsequent maintenance dose has varied from 0.1 to 0.4 mg. daily. In addition, despite the stated cumulative action of digitoxin, it has been necessary to redigitalize some patients with congestive failure at intervals of four to six months, even though they have been on large, apparently adequate, maintenance doses. When patients with auricular fibrillation become ambulatory close observation of the effect of exercise on the ventricular rate is necessary.[59–61] A sufficiently large maintenance dose should be administered so that exercise does not produce an excessive rise in ventricular rate.

In summary, the advantages of digitoxin are that it is a pure chemical that is stable and does not require bio-assay and that it is completely absorbed from the gastrointestinal tract, so that the oral and intravenous doses are the same and interchangeable. Furthermore, the small amount of digitoxin necessary for digitalization permits administration of a large fraction in a single dose, with only a small incidence of local gastrointestinal irritation. The rapid onset of action makes for quick digitalization by the oral route so that intravenous administration is rarely necessary. The prolonged duration of action, like that of whole-leaf digitalis, makes for easy maintenance. It is thus the drug of choice when a purified preparation is desired. Since there is some evidence that various preparations of digitoxin differ in potency, it is advisable for the physician, as with whole-leaf digitalis, to use a single preparation with whose action and potency he is familiar. The cost of digitoxin is at present considerably more than that of whole-leaf digitalis.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 32521

PRESENTATION OF CASE

A forty-five-year-old schoolmaster entered the hospital because of an abdominal mass associated with crampy abdominal pain.

Thirty days before admission the patient had had a short attack of knifelike suprapubic pain that was accompanied by the passage of considerable gas by rectum. At that time he was en route from India to the United States. He had served in India for three years with the United States Army Air Force during which time he had felt entirely well and had had no tropical diseases. Examination had been carried out by a flight surgeon shortly before departure, and no abnormalities had been noted. On arrival in the United States the patient noticed the appearance of a lower abdominal mass. This was called to the attention of a physician, who found a nontender symmetrical mass in the suprapubic area about the size of a large grapefruit; this extended to the umbilicus. The patient was referred to a genitourinary consultant, who catheterized the bladder and found no residual urine. The mass did not change on catheterization. The patient was then referred to the hospital. On entry he stated that the day before admission he had felt nauseated and had vomited twice; this was the only episode of nausea and vomiting that had occurred. The bowel movements had been normal except that an unusual amount of gas had been passed by rectum; there had been no mucus or blood. There had been no urinary symptoms or weight loss.

The past history was irrelevant except for pneumonia in childhood and a tonsillectomy as a young man. The family history revealed that the patient's mother had died of diabetes, and his grandmother, of cancer.

Physical examination disclosed a well nourished patient in no acute distress. The lower abdomen was slightly protuberant. A large, hard, nodular tumor extended upward in the midline from the pelvis to the area of the umbilicus. It was quite fixed in position and seemed to be adherent to the abdominal wall. Some portions of the mass were slightly tender. Rectal examination was negative. The heart and lungs were normal.

The temperature was 98.6°F., the pulse 86, and the respirations 20. The blood pressure was 138 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 4,280,000, with a hemoglobin of 13 gm. per 100 cc., and a white-cell count of 18,300, with 82 per cent mature neutrophils, 7 per cent young neutrophils and 11 per cent lymphocytes. The urine was normal except for a + test for albumin in one specimen. The nonprotein nitrogen was 27 mg. and the serum protein 6.9 gm. per 100 cc. The chloride was 94 milliequiv. per liter. A stool specimen was brown and gave a negative guaiac reaction. Routine x-ray films of the chest were negative.

Roentgenographically, the kidneys appeared normal in size and position, and intravenous dye was promptly excreted by both kidneys. There was some distention of the right ureter and to a lesser extent of the left midureter, and there was delay in passage of the dye at the level of the sacrum (Fig. 1). The bladder shadow was compressed superiorly by what appeared to be an ill defined midline mass filling the basin of the pelvis. In the lateral view the right ureter appeared displaced anteriorly. There was a small calcified lymph node in the midabdomen. Visualized bones showed no evidence of intrinsic disease. There was spina bifida of the fifth lumbar vertebra without displacement. An attempted examination of the colon showed the sigmoid loop to be displaced downward and compressed toward the left, and barium could not be found beyond that point. It was stated that the films showed no definite evidence of intrinsic disease of the colon.

On the fourth hospital day proctoscopy revealed a sharp posterior angulation 16 cm. from the anus that stopped the progress of the instrument. The mucosa was normal, and there was no evidence of ulceration, bleeding or intrinsic tumor. Cystoscopy was attempted; the compression of the bladder from without prevented sufficient distention to enable its mucosa to be visualized.

Except for slight daily elevations of temperature to 99.5°F., there was no change in the patient's condition. On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GRANTLEY W. TAYLOR: May we see the x-ray films?

DR. JAMES R. LINGLEY: The margins of the mass are not well defined on the film, but the presence of a mass may be inferred from the evidence of marked pressure on the superior margin of the bladder, with flattening of the bladder shadow, and from the evidence of obstruction of both ureters. In the lateral view one ureter, in addition to being

dilated, is displaced anteriorly, suggesting a retroperitoneal origin for the mass. The barium-enema study is rather unsatisfactory, probably because the patient was unable to hold the barium. The column ends in the descending colon, and so far as I can make out, there is no evidence of intrinsic disease, although there is marked displacement, as described in the record.

DR. TAYLOR: This is a long history, and yet it includes few positive findings. The background of India is canceled out by the facts that no tropical diseases are mentioned and that the patient had always been well while there. The examination by the flight surgeon before departure from India, with the finding of no abnormalities, should probably not be seriously considered. I believe that the flight surgeons may have overlooked masses the size of a grapefruit or watermelon. The patient did have a mass when he arrived in this country, however, and was astute enough to recognize it himself. The only preceding episode was the brief attack of knifelike pain followed by the passage of flatus on the trip home. In the hospital, the patient felt nauseated and vomited. Otherwise, the only findings were the large hard, partly fixed mass in the pelvis and the elevation of the white-cell count to 18,300.

What caused the pelvic mass? The elevated white-cell count at once makes us wonder whether an inflammatory mass was involved. If this patient had been older and had presented x-ray evidence of a diverticulum, one would wonder if the mass had arisen from diverticulitis of the colon, which sometimes causes large masses. The surprisingly negative history of any relation to episodes of inflammation in the past, however, makes one doubt that. Similarly, an appendiceal abscess frequently gives rise to a large mass, but again there is nothing in the background except for one brief episode of pain. If we had to go seriously into the background of tropical diseases I should not know what to call a mass originating in a patient who had been in India. If he had been in South America, one would wonder about echinococcal disease in some form. Certainly against inflammatory disease is the absence of anything suggesting an inflammatory

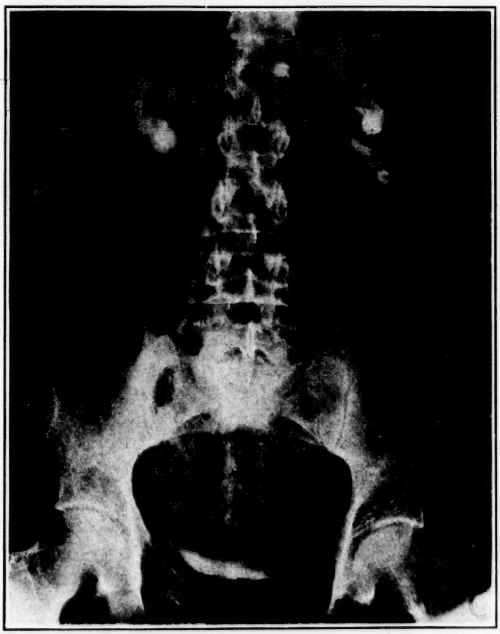

FIGURE 1.

process, except the elevation of the white-cell count and the slight rise of the temperature to 99.5°F. in the hospital.

So we move on to tumors. The only thing we can be grateful for in an otherwise confusing picture is that this patient was not a woman and that we do not have to consider the female genital tumors. It is bad enough as it is. The x-ray evidence regarding the location of the tumor is complicating in the sense that one ureter was pushed forward, suggesting a retroperitoneal origin for the mass. On the other hand, the sigmoid colon seemed to be knuckled backward when palpation was attempted, suggesting an intra-abdominal mass flexing the colon backward. It is hard to see how a retroperitoneal mass would do that to the colon.

From here on it becomes a matter of guessing what kinds of pelvic tumors occur in patients who are practically asymptomatic. We always fall back on the retroperitoneal fibrosarcoma as an explanation for many tumors, and that does not do much more than characterize the histology. We know little about the process, which is a rather frequent finding in a large hospital such as this; I suppose we have a number of them each year that are called retroperitoneal fibrosarcoma. As a rule, when such tumors achieve the size of the one in this case, there is evidence of vascular or lymphatic blockage, as well as a suggestion of associated edema of one extremity and evidence of stasis in the lymphatic or venous return. That is perhaps because the tumor not only causes pressure on the vessels but may actually invade them and propagate in them as a growing tumor thrombus.

A tumor that is frequently seen in this location is the chordoma — another tumor that we do not know a great deal about. As a rule, I believe that all such cases show some evidence of bone destruction because of their locus of origin. They are slow in their progress, and it seems likely that a chordoma that had achieved the size of the tumor in this case would have been observed for many years rather than a brief time. Dermoid cysts that originate in this part of the body are sometimes practically asymptomatic; they are usually symmetrical and smoothly outlined, and the nodular character of the tumor in this case argues against dermoid, unless secondary malignant degeneration had occurred.

Tumors of the lymphoblastic series are usually multiple; sometimes there is a large single tumor, which may appear as a retroperitoneal mass. The negative x-ray findings justify us in ruling out some of the other things that occur to one asked to define the cause of a pelvic tumor. Sometimes, ectopic kidneys, which are infected or otherwise, may become quite large, causing a great deal of trouble for the patient. Bone tumors and chondrosarcoma often reach enormous size and may be located in this region. The primary tumors of the bowel rarely develop to this extent, and certainly without bowel symptoms they are practically unheard of. Consequently, this tumor must have occurred in tissues that are found in this general region, having no association with any specific organ, if neoplasm is to be regarded as accounting for this patient's symptoms.

Could neoplasm account for the elevation of the white-cell count and temperature? I think that in certain circumstances it could, but the white-cell count was rather high and the young neutrophils suggest that an active inflammatory process was going on somewhere. One neoplasm that I did not allude to, — and I swing back to the appendix again, — is a carcinoid, which may involve the appendix and may become a tumor of significant size, although I have never heard of any carcinoid nearly approaching this one in extent. If I must commit myself, I think that the diagnosis is more probably appendiceal abscess, with a mass around it, than a primary pelvic neoplasm. I base that statement partly on the rapid development, partly on the fact that there was not much in the way of pressure obstruction of the circulatory apparatus of the lower extremities and partly on the specific character of the tumor as described on palpation, since it was much higher in the pelvis than a great many of the tumors to which I have referred. They usually occupy the true pelvis, not the pelvic canal, and are palpable on rectal examination, whereas this tumor was well up and above that, although in the x-ray film it appears to descend fairly low.

A PHYSICIAN: Could the right ureter have been drawn forward rather than pushed out by the mass?

DR. TAYLOR: I should think that it could.

DR. ROLF LUFT*: In Sweden, years ago, a nurse in a hospital had a large tumor mass in the pelvis that was described as Symmer's disease and that originated in the retroperitoneal lymph nodes.

DR. TRACY B. MALLORY: Symmer's disease is usually called giant follicular lymphoma in this country.

CLINICAL DIAGNOSES

Sarcoma compressing rectosigmoid, bladder and ureters.

Hydronephrosis.

DR. TAYLOR'S DIAGNOSIS

Appendiceal abscess.

ANATOMICAL DIAGNOSIS

Lymphoblastic lymphoma of small bowel.

PATHOLOGICAL DISCUSSION

DR. CLAUDE E. WELCH: The differential diagnosis on the surgical service was not so thorough as Dr.

*Of Stockholm, Sweden.

Taylor's, nor did we take into consideration so many points. We differed when we came to the final analysis and swung in favor of tumor instead of appendiceal abscess, thinking that it probably was a retroperitoneal sarcoma. The only x-ray examination that we did not make was a small-bowel series. At that time we could not visualize a primary lesion of the small bowel that would cause so much difficulty without intestinal obstruction. In retrospect, we should have considered the special tumor of the small bowel that is characterized by distended bowel and not by obstruction.

When we opened the abdomen the first thing visible was massive edema anterior to the peritoneum. Within the peritoneal cavity there was a greatly dilated, perforated loop of ileum. There was a large abscess walled off by the sigmoid. There was a sharp demarcation between normal small bowel and the tumor area; the latter was about 60 cm. long. There were also huge lymph nodes in the mesentery, some being as large as 3 cm. in diameter. When we saw the gross specimen we were fairly sure of the diagnosis of lymphoma. While the pathologist was examining the tumor, we went ahead with resection of the small bowel and anastomosis.

DR. MALLORY: Frozen section of the tumor showed obvious neoplastic disease, which we thought was lymphomatous. That was confirmed by the sections of fixed tissue. Both the bowel wall and the mesentery were diffusely invaded by tumor composed almost entirely of immature lymphocytes, and we classified the lesion as lymphoblastic lymphoma.

Were you able to verify whether or not the retroperitoneal tissues were involved, Dr. Welch?

DR. WELCH: We could not tell because of the tremendous amount of edema.

DR. MALLORY: It had extended so far back into the mesentery that I think it probable that they were.

DR. WALTER BAUER: Was this a lymphoblastic type of lymphoma arising in the small intestine?

DR. MALLORY: I cannot say whether it arose in the small intestine and invaded the mesentery secondarily, or whether it was in the mesenteric lymph nodes and involved the small bowel.

DR. BAUER: And there was never more interference of bowel habit than that mentioned in the record?

DR. MALLORY: In lymphoblastoma I have seen 12 to 50 cm. of small bowel thickened to the appearance and almost the stiffness of a rubber hose, with no intestinal symptoms.

DR. BAUER: Is there a type of lymphoblastoma that is confined to the small intestine and may be cured by resection? If so, what type is it?

DR. MALLORY: Any one of the types. We have seen isolated lymphomatous tumors with prolonged cures after resection in the stomach, the small bowel and the large bowel.

DR. BAUER: Have the cures lasted five to twenty years?

DR. MALLORY: I am sure that I have seen cures as long as ten years. Beyond that I do not want to say.

DR. BAUER: Is that equally true with any of the lymphomatous tumors, the reticulum-cell, the lymphocytic or the lymphoblastic type?

DR. MALLORY: One probably has a better chance with a reticulum-cell sarcoma, but I have seen such cures with several types.

DR. BENJAMIN CASTLEMAN: Several years ago Dr. Gall* reported a series of such cases that had been observed here.

DR. TAYLOR: I should like to ask Dr. Welch if the mass was primarily inflammatory or whether it chiefly consisted of tumor.

DR. WELCH: It was practically all an inflammatory mass.

*Gall, E. A., and Mallory, T. B. Malignant lymphoma: clinicopathologic survey of 618 cases. *Am. J. Path.* 18:381-429, 1942.

CASE 32522

PRESENTATION OF CASE

A sixty-two-year-old housewife entered the hospital because of persistent drainage from a cecostomy.

About five years before admission the patient first began having attacks of abdominal pain in the left lower quadrant. These lasted a day or two and were accompanied by a feeling of tenesmus and by loose stools. Between attacks there was no discomfort. The stools gradually became smaller in size but never contained blood and were never black. About fifteen weeks before admission, during an unusually severe attack of pain, the left side of the abdomen was found to be swollen. At that time an operation was performed. The only available details were that an incision had been made in the left lower quadrant, and that a cecostomy had been performed. After the operation the patient was too weak to do more than sit up in a chair for a part of each day. The cecostomy functioned well. Subsequently, a small amount of fecal matter and some mucus were passed by rectum, but never any blood. There had been a weight loss of 13 to 15 pounds in the two months preceding admission. Except for occasional pain on motion of the knees and elbows and slight exertional dyspnea, there were no complaints.

Physical examination showed a moderately obese woman. The abdomen was slightly distended. There was a well healed incision in the left lower quadrant. There was a functioning cecostomy whose mucosa was widely everted. Vaginal examination revealed a normal cervix and a uterus whose fundus was barely palpable in normal position.

There was induration high in the left vault. On rectal examination there appeared to be a mass fixed high to the lateral pelvic wall on the left that did not involve the rectal mucosa. Proctoscopy for a distance of 15 cm. showed a normal mucosa. Further progress of the proctoscope was stopped by angulation of the bowel.

Examination of the blood revealed a hemoglobin of 12.4 gm. per 100 cc. and a white-cell count of 10,200, with 69 per cent neutrophils. The urine gave a + test for albumin, and rare granular casts, 2 red cells and 50 white cells per high-power field were found in the sediment. Barium filled the rectum and distal sigmoid readily. In the mid-sigmoid there was an area of constant narrowing, extending for a distance of about 8 cm. (Fig. 1); in one portion there appeared to be an absence of the mucosa in a small area, but the remainder of the mucosa looked normal. There was an indefinite

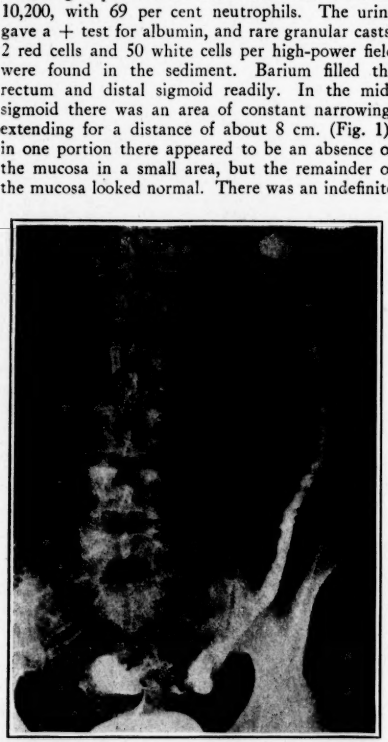

FIGURE 1. *Plain Film of Abdomen following a Barium Enema.*

suggestion of a shelf defect distally and of rounded, filling defects in the lower portion of the lesion.

An operation was performed on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. WALTER GARREY: It might be instructive to comment briefly about the history and physical findings before we look at the x-ray films. The patient was a sixty-two-year-old woman who for five years had had brief attacks of pain in the left lower quadrant lasting a day or two, with a feeling of tenesmus and the passage of loose stools. This certainly suggests a recurring inflammatory process in the bowel. Then the patient gave evidence of a gradually increasing degree of chronic, low, large-bowel obstruction — she was definite that the stools had become smaller in size. She had never noticed any blood, although, of course, she may have overlooked it. She had a severe attack of pain and was operated on; apparently, the lesion found was such that the surgeon decided merely to relieve the large-bowel obstruction by doing a cecostomy but did not defunction the bowel with a colostomy. Four months later she was admitted to this hospital, where a mass was found high up in the left pelvis or low in the left lower abdomen. She had a slight degree of anemia and claimed to have lost a little weight. I suppose that the urine was a voided specimen; if so, the white-cell count means little.

May we see the x-ray films?

DR. JAMES R. LINGLEY: This area in the colon, just above the midsigmoid, shows a definite narrowing. No diverticulums are visible, and on the inferior margin of the bowel there appear to be round defects. I cannot be too sure of the mucosa in that film, but I think that there is definite evidence of masses in the bowel wall.

DR. GARREY: But there is sufficient filling of the rest of the colon, so that if there had been diverticulums farther up the colon they would have shown?

DR. LINGLEY: I think that they would have shown.

DR. GARREY: Is this an annular lesion?

DR. LINGLEY: No; I think that it involves chiefly the lower margin of the bowel and that there is intact mucosa above.

DR. GARREY: Is there a definite ulcer at this spot?

DR. LINGLEY: The fluoroscopist described an ulcer. I cannot be certain from the films.

DR. GARREY: This history could be explained by an inflammatory process because of the recurring attacks for a long time. Far and away the most frequent of all these is a diverticulitis of the sigmoid. The midsigmoid is the likeliest location for diverticulitis, and the chronic obstructing form of diverticulitis easily gives an 8-cm. cylindrical obstructing lesion with a normal mucosal pattern, the obstruction being due to a woody-hard, inflammatory reaction in the walls of the bowel. The fact that no blood was noted fits perfectly well with diverticulitis. In the different series of cases of diverticulitis reported, blood has been found in from 6 to 30 per cent. One expects to find blood in cases of carcinoma — even if the patient has not noted it, it is usually found on chemical testing. We have no information whether such tests were done. In over 90 per cent of cases that have diverticulitis in the midsigmoid one or more diverticulums are found elsewhere in the colon. None were found in this case, despite fairly good filling. The fact that the obstruction produced by this lesion did not subside

after a cecostomy is no contraindication to the diagnosis of chronic obstructing diverticulitis. In the first place, the bowel was not defunctioned, and many cases on record go for even twelve months with little relief in the inflammatory thickening of the bowel after cecostomy.

What other conditions should we consider? There was an unusual case, seen in this hospital a few years ago and discussed at one of these conferences by Dr. McKittrick,[1] of endometriosis involving the sigmoid in a woman past the menopause, but the area of endometriosis and narrowing of the sigmoid was small. With this 8-cm. obstruction, or nearly complete obstruction, intussusception of that area is certainly a possibility but a rare and most unusual eventuality.

Could this have been a tuberculous inflammatory lesion? I think that the size and the lack of a large ulcer, as well as the location in the left rather than in the right colon, are against that diagnosis.

Could this have been any form of benign tumor? Such tumors are extremely rare in the colon. Lipomas occur but certainly do not give an 8-cm.-long cylindrical type of obstruction. I do not believe that this was a lipoma.

Could the obstruction have been due to something extrinsic to the colon and involving it secondarily? It is possible that cancer of the ovary invaded the sigmoid, but after such a long period, I should expect the patient to have had ascites or signs of dissemination rather than a localized process in the bowel itself.

Another possibility is that, over this long period, some premalignant lesion, such as an adenomatous polyp, was present and that eventually a slowly growing neoplasm developed and invaded the bowel, infiltrating upward in the mucosa, so that part of the mucosal pattern was visible and yet there was some ulceration. I think that that is a good possibility. We are not told whether any tests for blood were made on the stools.

Dr. Tracy B. Mallory: There is no record of any tests on the stools.

Dr. Garrey: Could this have been a diverticulitis of the chronic obstructing type, accounting for the history of recurring episodes, with the subsequent development of a carcinoma of the sigmoid, so that there was a double diagnosis? That is possible, and it is interesting that in a series of 40 cases recently reported by Dr. Young,[2] 2 such examples of double lesions were not correctly diagnosed either by x-ray or other studies beforehand. In these exercises, however, it is safer to make one diagnosis than two. Since we are told that there were nodular filling defects in the bowel and an area in which there was normal mucosa and still another area in which there was ulceration, I shall call this carcinoma, but I think that diverticulitis could perfectly well explain the entire picture.

Dr. Arthur W. Allen: Dr. Garrey has covered this situation exceedingly well. I should like to emphasize one of his last statements. I was afraid that he was not going to mention the diagnosis of carcinoma of the sigmoid, with coincident diverticulitis. That is a fairly frequent finding. Every series of reported cases of diverticulitis or diverticulosis of the sigmoid includes a certain number of such cases. There is a good deal of disagreement concerning the significance of bleeding in the differential diagnosis. Dr. Harvey Stone is sure that bleeding can occur from diverticulitis alone. Dr. Vernon David, on the other hand, states that with bleeding in a case of diverticulitis of the sigmoid one must assume that carcinoma is present. Both are right to a certain extent. It may interest Dr. Garrey to know that the surgeon who first explored this patient and did the cecostomy made the diagnosis of carcinoma; in the acute stage such a diagnosis is frequent. It is difficult to tell by palpation or exploration whether the lesion is inflammatory or neoplastic. We thought that this woman had cancer, but we were wrong. It is only fair to say that we were influenced to some extent by the x-ray finding of the mucosal defects and so forth. It could well have been carcinoma on the basis of the history, in spite of the diverticulitis, as Dr. Garrey has pointed out.

Clinical Diagnosis

Carcinoma of sigmoid.

Dr. Garrey's Diagnosis

Carcinoma of sigmoid. superimposed on diverticulitis.

Anatomical Diagnosis

Diverticulitis of sigmoid.

Pathological Discussion

Dr. Mallory: The resected specimen showed a localized area of diverticulitis, with a chronic inflammatory process in the bowel wall accounting for the contraction of the bowel lumen. There were numerous diverticulums, all solidly plugged with fecaliths, which explains why the barium did not fill them. There was no evidence of neoplasm.

References

1. Case records of the Massachusetts General Hospital (Case 22412). *New Eng. J. Med.* 215:678-680, 1936.
2. Young, E. L., and Young, E. L., III. Diverticulitis of colon: review of literature and analysis of ninety-one cases. *New Eng. J. Med.* 230:33-38, 1944.

An index of the diagnoses and discussers of the Case Records for the year 1946 will be found elsewhere in this issue of the *Journal*.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, two weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

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HAPPY NEW YEAR

CHRISTMAS and New Year, as was suggested on this page last week, travel well together. They are as companionable as Damon and Pythias, as Troilus and Cressida, as ham and eggs; as inseparable in our minds as David and Goliath or as a pick and its shovel. They are more than that: they are almost, although not quite, identical images that have been carelessly imposed on each other. There they are, as like as two peas, but the edges are a little blurred.

They could well have been identical if our old time astronomers had been able to calculate a little more closely, for they both mark the turning of the season, only both are a little late — an almost human failing. It is the Christian Church that attached the religious significance to the pagan festival that is now Christmas. The New Year, too, has its pious resolutions.

Perhaps it is just as well that Christmas and New Year are a week apart, from a practical point of view. Some heads would hardly be equal to eggnog in the morning and wassail in the afternoon. The present juxtaposition, moreover, without exact identification, like the blurred image, gives us what we really want in midwinter — not simply a holiday, too intense, but a holiday season.

The idea of the Happy New Year, as a greeting, is a good one. No one has really expected, during the last five thousand years or so since civilization began, that the impending year would really be a happy one, and it is surprising how often so many of us have been agreeably disappointed. There has always been someone on every street corner waiting for the world to fall apart, and as a rule most of these, too, have had to turn their grudging footsteps homeward.

Our prediction is that the coming year will bring a number of industrial and international crises, a certain amount of snow and rain and some fair weather and a good deal of hollering by all concerned. At its end we shall find ourselves in port with a few loose rivets, and continue making gloomy forecasts for 1948.

And so, with considerable assurance, we wish all our readers — a select group — our usual Happy New Year!

SYPHILIS AND PENICILLIN

MANY reports have been published indicating the response of syphilis to penicillin therapy. Physicians in general have been quick to adopt this new medicinal agent, and the laity has developed an enthusiasm about its use in syphilis and other diseases that may require some curbing. It is well, therefore, to review with care some of the problems arising in the course of penicillin therapy, such as is done elsewhere in this issue of the *Journal*. Problems arise in connection with the penicillin-resistant case and in matters of relapse, reinfection and reactions. Public-health aspects, including the question of the returning veteran and marriage, are topics of concern in connection with penicillin

therapy. These and other matters must be carefully considered, especially in the light of the gradually increased dosage of penicillin that is being recommended from time to time following careful studies of treated cases. Some of these patients did not receive enough penicillin to cure their syphilis and have relapsed or will relapse.

The matter of relapse is of special significance. In the group of clinics sponsored by the National Research Council and the United States Public Health Service the cumulative percentage failure at the end of eleven months after treatment varied from 15 per cent with a dosage of 2,400,000 units of penicillin to 62 per cent with one of 600,000 units.[1] About 10 per cent of these failures were actually due to reinfection, but the rest were relapses. Various treatment schedules were used in the different co-operating clinics, and in general it can be said that there were fewer failures when both arsenic and bismuth were used in combination with the penicillin.

Another complication has been added by the changing character of commercial penicillin.[2] Various fractions of penicillin have been found and designated G, X, F and K. Penicillin K is relatively inefficacious, since it is rapidly destroyed in the body; this assumes significance because of the fact that certain commercial penicillins have recently shown an increasing content of penicillin K. It is also not known as yet whether increasing purification of penicillin removes some of the substances that have great therapeutic activity.

As a result of reviewing these cases in the various co-operating clinics it has been suggested that for seronegative primary syphilis the minimum dose of the at-present-available penicillin should be not less than 3,600,000 units, given intramuscularly in doses of 40,000 to 60,000 units at two-hour or three-hour intervals. For seropositive and early secondary syphilis a dose of not less than 5,400,000 units is recommended. If a relapse occurs, arsenic and bismuth should also be given when the course of penicillin is repeated. Penicillin by mouth is not advocated. Thus, the treatment of syphilis by penicillin has repeatedly been modified as further study of treated cases has progressed.

Emphasis is placed on the fact that the present recommendations are only tentative and are subject to revision as the results of treatment are further studied. The eventual value of penicillin in syphilis is still uncertain, and its ultimate status will not be established for several years to come. To be sure that syphilis has been successfully treated by any new procedure requires a long period of observation, measured in terms of years, not months. Every physician thus has a particular responsibility for the careful follow-up, serologic and clinical, over a period of years of every penicillin-treated case of syphilis that he sees, whether the penicillin was received in civilian life or during military service.

REFERENCES

1. Committee on Medical Research and United States Public Health Service. Treatment of early syphilis with penicillin. *J. A. M. A.* 131:265-271, 1946.
2. Committee on Medical Research, United States Public Health Service and Food and Drug Administration. Changing character of commercial penicillin: with suggestions as to use of penicillin in syphilis. *J. A. M. A.* 131:271-275, 1946.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

GROUP DONATIONS TO THE MASSACHUSETTS BLOOD DONOR PROGRAM

Many social and fraternal organizations are obtaining the benefits of the services and protection offered by the Massachusetts Blood Donor Program by making group donations when the Mobile Unit visits their community. By having at least 10 per cent of the total membership of the organization donate to the program, every member in the entire group becomes eligible to receive whole blood, plasma or fractions when needed.

Details of the plan for group participation are simple. Any organization desiring to donate in a body should communicate with its local Red Cross chapter, expressing a willingness to take part in the program. Arrangements for the registration of and appointments for donors can be worked out jointly by group directors and the registration committee in the local chapter.

The quota of one donor for each ten members is only temporary and will be adjusted from time to time as the needs of the various organizations change. If it is discovered that a quota of 10 per cent does not provide enough blood to meet the requirements of a particular group, the quota will be increased. On the other hand, if there is a comparatively small demand from any group, its quota will be accordingly reduced.

MOBILE-UNIT VISITS

The Mobile Unit of the Massachusetts Blood Donor Program will make the following visits during the latter half of January:

PLACE	DATE
Chicopee	January 21
Springfield	January 22 and 23
Westfield	January 24

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Lowell	January 3	Albert H. Brewster
Salem	January 6	Paul W. Hugenberger
Haverhill	January 8	William T. Green
Brockton	January 9	George W. Van Gorder
Gardner (Worcester subclinic)	January 14	John W. O'Meara
Pittsfield	January 15	Frank A. Slowick
Worcester	January 17	John W. O'Meara
Fall River	January 20	David S. Grice
Springfield	January 21	Garry deN. Hough
Hyannis	January 23	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

MISCELLANY

HUNDREDTH ANNIVERSARY OF A. M. A.

The American Medical Association is going to celebrate its centennial in Atlantic City on June 9-13, 1947, and elaborate plans are being made for this celebration. Only fellows and invited guests are eligible to attend. Membership in a state society is the primary qualification for fellowship in the Association. Fellowship dues and subscription to the *Journal of the American Medical Association* are both included in one annual payment of $8.00, which is the cost of the periodical to subscribers who are not fellows.

Anyone who is not a fellow and plans to attend the Atlantic City session, which will be a milestone in medical history, can save himself considerable time and confusion when registering, if he will write now to the American Medical Association, 535 North Dearborn Street, Chicago 10, asking if he is eligible to become a fellow.

NOTE

The following appointments to the teaching staff of Harvard Medical School were recently announced: Henry Freeman Allen, of Boston (A.B. Harvard University 1939, M.D. Harvard University 1943), fellow in ophthalmic research; Albert Cisler Biegel, of Denver, Colorado (A.B. University of Colorado 1941, M.D. Harvard University 1944), fellow in ophthalmic research; David Lukens Coffin, of Boston (V.M.D. University of Pennsylvania School of Veterinary Medicine 1938), research fellow in pathology; Leonard Paul Eliel, of San Francisco, California (S. B. Harvard University 1936, M.D. Harvard University 1940), research fellow in pediatrics; Kenneth Austin Evelyn, of Montreal, Canada (S.B. McGill University 1932, M.D., C.M. McGill University 1938), research associate in medicine; Geoffrey Alan Gilbert, of Birmingham, England (M.A. Emmanuel College, Cambridge 1939, Ph.D. Emmanuel College, Cambridge 1943), research fellow in physical chemistry; Avram Goldstein, of New York City (A.B. Harvard University 1940, M.D. Harvard University 1943), assistant in pharmacology; John Harold Hanks, of Newton Center (S.B. Allegheny College 1928, Ph.D. Yale University 1931), lecturer on bacteriology and immunology; Harper Keith Hellems, of Lewisburg, West Virginia (M.D. University of Virginia 1943), research fellow in medicine; Elliott Samuel Hurwitt, of Brookville, Pennsylvania (A.B. Harvard University 1933, M.D. Harvard University 1937), research fellow in pathology; Robert Kaye, of Philadelphia, Pennsylvania (A.B. Johns Hopkins University 1939, M.D. Johns Hopkins University Medical School 1943), assistant in pediatrics; Frederic Koller, of Zurich, Switzerland (A.B. College of Trogen 1925, M.D. University of Geneva 1931, Privat-Dozent University of Geneva 1940, associate in medicine, University of Zurich 1944), research fellow in medicine; Evelyn Lenore Oginsky, of Liberty, New York (A.B. Cornell University 1938, S.M. University of Chicago 1939, Ph.D. University of Maryland 1946), research fellow in bacteriology and immunology; Francis Thomas Garnet Prunty, of London, England (M.A. University of Cambridge 1935, M.D. University of Cambridge 1944), research fellow in medicine; Henrik Seyffarth, of Oslo, Norway (M.D. University of Oslo 1941), research fellow in neurology; William McLean Wallace, of Hyde Park (A.B. University of Pennsylvania 1934, M.D. University of Pennsylvania 1938), assistant in pediatrics; Stanley Moore Wyman, of Cambridge (A.B. Harvard University 1935, M.D. Harvard University 1939), assistant in radiology; and Leona Zacharias, of Belmont (A.B. Barnard College 1927, A.M. Columbia University 1928, Ph.D. Columbia University 1937), instructor in ophthalmic research.

BOOK REVIEWS

One Hundred Years of Gynaecology, 1800-1900: A comprehensive review of the specialty during its greatest century, with summaries and case reports of all diseases pertaining to women. By James V. Ricci, M.D. 4°, cloth, 651 pp. Philadelphia: The Blakiston Company, 1945. $8.50.

This monumental work is a complement, sequel and conclusion to the distinguished author's previously published *Genealogy of Gynaecology*, which summarized the first thirty-eight hundred years of the history of the specialty. The present volume, both a historical document and a reference book, encompasses the gynecologic literature of the nineteenth century, the greatest of its periods. This literature is not merely immense — it is gigantic. The author has accomplished his colossal objective triumphantly and has produced not a bibliographic catalogue but an integrated story of the development of gynecology to its present status. "Dr. Ricci's zeal and industry," says Dr. Claude Heaton in his introduction, "have crystallized in a work which will for many years to come be the most complete source book on the literature pertinent to the history of gynaecology." The volume concludes with a fragment "Memoirs in Gynaecology" from Dr. Henry Clarke Coe, who was to have contributed a chapter on gynecologic trends since 1870.

Fractures and Orthopaedic Surgery for Nurses and Masseuses. By Arthur Naylor, Ch.M., M.B., M.Sc., F.R.C.S. (Eng.), F.R.C.S. (Edin.). With a foreword by Ernest Finch, M.D., M.S. (Lond.), F.R.C.S. (Eng.). 8°, cloth, 288 pp., with 243 illustrations. Baltimore: The Williams and Wilkins Company, 1945. $5.00.

Anyone who attempts to write a textbook for nurses finds the task of selection of material most difficult: a little knowledge is a dangerous thing, and for this reason, discussions must not be too detailed but must be complete enough that intelligent nursing care can be given. In this book the author has given a satisfactory exposition of fractures and their treatment; this is the best section of the volume. The chapter on orthopedic apparatus is well written and profusely illustrated. The other sections merely catalogue a number of conditions that the orthopedic surgeon treats. Discussion of these conditions is inadequate for a nursing textbook on orthopedic surgery. This book should be particularly helpful to the nurses assigned to the outpatient or inpatient fracture service of a hospital.

Clinical Traumatic Surgery. By John J. Moorhead, M.D., D.Sc. 8°, cloth, 747 pp., with 500 illustrations. Philadelphia: W. B. Saunders Company, 1945. $10.00.

This volume is based on the author's experience of over forty years with the surgery of trauma as medical director of the New York City Transit System and consulting surgeon to numerous New York hospitals. It is written frankly in the first person singular, since "the average reader seeks the opinion of the writer," and therefore contains almost no references to the literature. Safe and simple methods of treatment are emphasized throughout, and the book contains much common sense. The discussion of ruptured intervertebral disk is particularly good. The author's opinion, however, is often considerably at variance with generally accepted standard practice and the experience of others. For example, few surgeons would agree that irrigation of fresh open wounds with alcoholic iodine solution should be recommended as a first-aid measure, or that chromic catgut is satisfactory for closure of the skin after the open reduction of fractures. Nowhere in the chapters on shock

and burns are hematocrit or blood-protein determinations mentioned. For the treatment of contusions the external application of soapsuds is advised and no mention is made of cold and compression. Tracheotomy rather than bronchoscopy is recommended for the removal of foreign bodies from the bronchi. The pages on thrombosis and embolism contain no discussion of heparin, dicoumarol or venous ligation.

Although the book will be of interest to others working in the same field, it cannot be recommended for teaching or as a clinical guide for house officers and residents.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Men Under Stress. By Roy R. Grinker, M.D.; and John P. Spiegel, M.D. 8°, cloth, 484 pp. Philadelphia: The Blakiston Company, 1945. $5.00.

This study on war neuroses is based on the authors' experience in working with combat soldiers overseas in an active theater of operation and with returnees hospitalized for rehabilitation.

The Eternal Ones of the Dream: A psychoanalytic interpretation of Australian myth and ritual. By Géza Róheim, Ph.D. 8°, cloth, 270 pp. New York: International Universities Press, 1945. $4.50.

Dr. Róheim, in this monograph, attempts to apply the most recent developments in psychoanalytic theory to the latest available anthropologic data on the natives of Australia, who are among the most primitive human beings still living in the world. The author investigates the origin of myth, particularly the relation of myth to history and ritual, symbolism and nature mythology. He evolves an entirely new theory on circumcision and discusses extensively the interrelation of dreams, day dreams and historical traditions with myths and rituals.

An Introduction to Medical Science. By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), professor of pathology and bacteriology, University of Toronto. Third edition, thoroughly revised. 8°, cloth, 366 pp., with 125 illustrations. Philadelphia: Lea and Febiger, 1945. $3.50.

This standard manual for nurses has been revised, and the size has been increased by eight pages. A new chapter has been added on the principles of treatment, dealing with such general matters as rest, the sulfonamides, penicillin, immunotherapy, organotherapy and physiotherapy. New material, including the Rh factor, the relation of sex hormones to cancer of the prostate and disseminated sclerosis, has been added, and the chapter on vitamins has been brought up to date. The newer nomenclature of bacteria has been used. The material is well organized. The book is well printed on good paper, and should prove valuable, not only to nurses but also to other professional medical workers and to medical librarians who have need of a concise manual on medicine.

Studies in Biophysics: The critical temperature of serum (56°C.). By Lecomte du Noüy, D.Sc., director of the Laboratory of Molecular Serology, University of Paris. 8°, cloth, 185 pp., with 89 illustrations. New York: Reinhold Publishing Corporation, 1945. $3.50.

This monograph is based on a large amount of experimental work, in which a number of new facts have been brought to light. These facts explain the fundamental problems relating to the mechanism of immunologic reaction and also disclose new problems as yet unsolved. The author has formulated a new hypothesis of a serum molecularly dispersed, comprising albumin, globulins, lipoids and so forth, in a true solution, either in a state of more or less gradual combinations or free, in contradistinction to the hypothesis of colloidal serum. The author concludes that alexinic activity is a property belonging to the protidolipoidic complexes, which are molecularly dispersed and which constitute the serum, and not to a separate body. He calls attention to twelve distinct physical phenomena occurring in serum when heated to around 56°C. and concludes that there are profound modifications in the structure of the proteins and of the lipo-protidic complex at around 55 to 56°C. This same temperature brings about the destruction of alexin, and therefore the author concludes that the disappearance of alexin is related to the structural clinical modification determined by heat in a serum molecule as a whole. This monograph should be in all medical-school libraries and reference and bacteriologic collections.

Textbook of Obstetrics: Designed for the use of students and practitioners. By Henricus J. Stander, M.D., professor of obstetrics and gynecology, Cornell University Medical College, obstetrician and gynecologist-in-chief, New York Hospital, and director, Lying-In Hospital, New York City. Stander's third revision. 8°, cloth, 1277 pp., with 739 illustrations. New York: D. Appleton-Century Company, Incorporated, 1945. $10.00.

This new edition of Dr. Stander's textbook, designed for students and practitioners, has been thoroughly revised and brought up to date. This work represents the ninth edition of *Williams Obstetrics*, first published in 1902, but since it embodies the teaching and practice of Dr. Stander, the title has been changed. This standard work is recommended for all medical libraries and all physicians practicing obstetrics.

A Textbook of Surgery: Compiled from lectures and other writings of members of the Surgical Department of the Harvard Medical School. By John Homans, M.D. With a special bibliographic index and with 530 illustrations by Willard C. Shepard and others. 8°, cloth, 1278 pp. Springfield, Illinois: Charles C Thomas, 1945. $8.00.

This sixth edition of an outstanding work on surgery, first published in 1931, has been thoroughly revised, despite the fact that the text pagination is practically unaltered. Much older and out-of-date material has been deleted and over 188 pages of new material have been added. New surgical developments based on war experience have been incorporated throughout the text. The historical approach to the various surgical subjects has been retained, and a bibliographic, historical index of sixty-eight pages is appended to the text. A comprehensive subject index concludes the volume. This work should be in the collections of all those interested in surgery, as well as in all medical libraries.

Studies from the Rockefeller Institute for Medical Research. Reprints. 4°, paper. Vol. 127, 605 pp., 1945. Vol. 128, 613 pp., 1946. New York: The Rockefeller Institute for Medical Research.

These two volumes contain the results of investigations conducted in the Rockefeller Institute and elsewhere under its grants and originally published in various serials and here brought together for convenient reference. Each volume has an index of authors and subjects.

The Physiological Basis of Medical Practice: A University of Toronto text in applied physiology. By Charles H. Best, C.B.E., M.A., M.D., D.Sc. (Lond.), F.R.S. and F.R.C.P. (Can.), professor and head, Department of Physiology, and director, Banting-Best Department of Medical Research, University of Toronto; and Norman B. Taylor, V.D., M.D., F.R.S. (Can.), F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Eng.) and L.R.C.P. (Lond.), professor of physiology, University of Toronto. Fourth edition. 4°, cloth, 1169 pp., with 497 illustrations. Baltimore: The Williams and Wilkins Company, 1945. $10.00.

This fourth edition of a standard textbook is published in a new two-column format that necessitated an entire resetting of the type. The majority of the illustrations have been reduced to one-column width, and a number of figures have been added and others redrawn. The work has been revised by the addition of new material, and some old mate-

rial has been deleted. Fifty-eight pages of references to the various chapters are appended to the text. A large, comprehensive index concludes the volume. The text is printed in two sizes of type, the smaller of which is rather difficult to read, but is used for less important material. This work should prove valuable to all practicing physicians for reference.

Classic Descriptions of Disease: With biographical sketches of the authors. By Ralph H. Major, M.D., professor of medicine, University of Kansas School of Medicine. Third edition. 4°, cloth, 679 pp., with 158 illustrations. Springfield, Illinois: Charles C Thomas, 1945. $6.50.

This third edition of a standard work in the field of the history of medicine, first published in 1932, has been revised by the addition of several new selections, and a bibliography has been added for the first time. Dr. Major has made two hundred and eighty-seven selections from the original accounts of one hundred and ninety-five physicians of all countries whose contributions and discoveries in the field of clinical medicine have been outstanding. These accounts are either the first known, one of the earliest or one of the most interesting accounts in question. The whole field of clinical medicine is covered from the time of the Papyrus Ebers, one thousand years before Hippocrates, to modern times. The work is divided into ten subject sections which are preceded by a historical summary and often by short biographic sketches. The original accounts have been translated into English wherever necessary, and the text is illustrated with carefully chosen portraits and facsimiles of titles and texts and drawings of apparatus. The book should be in all medical libraries, as well as in the collections of physicians interested in the history of medicine.

Psychiatry in Modern Warfare. By Edward A. Strecker, M.D., Litt.D., LL.D., professor of psychiatry and chairman of the department, University of Pennsylvania School of Medicine; and Kenneth E. Appel, Ph.D., M.D., Sc.D., assistant professor of psychiatry and chief of clinic, University of Pennsylvania School of Medicine, and lecturer in psychiatry, School of Neuropsychiatry, United States Naval Hospital, Philadelphia. 12°, cloth, 88 pp. New York: The Macmillan Company, 1945. $1.50.

The modern aspects of psychiatry as applied to the disasters associated with war are reviewed. The text is sound, and the book can be recommended. Although brief, it contains much that is pertinent to present conditions.

Diseases of the Nervous System. By F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P. (Lond.), D.Sc. (hon.), physician in charge of the Neurological Department, University College Hospital, London, physician to the National Hospital for Nervous Diseases, Queen Square, neurologist to the Hospital for Tropical Diseases, London, and to the Seamen's Hospital, Greenwich, and fellow of University College, London. Fourth edition. 8°, cloth, 360 pp., with 51 illustrations. Baltimore: The Williams and Wilkins Company, 1945. $4.50.

This popular small book, designed for practitioners and students, has passed into its fourth edition during the war years, a tribute to the soundness of the author's contribution. Some new material has been added, but in general the book remains as it was when first issued — a sound résumé of the subject, with emphasis on the clinical aspects of neurology. The author has been reasonably successful in keeping the book up to date, but the task is not an easy one and some modern advances are not given full recognition. Conservatism, however, is the keynote of the book and perhaps its most valuable asset. This volume, as a brief text of value to the clinician, can be given unqualified approval.

Take It Easy: The art of conquering your nerves. By Arthur G. Mathews. 8°, cloth, 239 pp., with 26 symbolical illustrations. New York: Sheridan House, 1945. $2.98.

The author has attempted to express in lay terms the present conception of neuroses and their treatment. In addition to the text he has used simple diagrams. In general his book is sound, but oversimplification detracts from its value. It is not a book that should receive unqualified recommendation.

NOTICES

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Friday, January 3 — Pulmonary Disease in Modern Industry. Dr. Harriet Hardy.
Wednesday, January 8 — Motion Picture: Energy Release from Food.
Friday, January 10 — Sterility. Dr. Somers Sturgis.
Wednesday, January 15 — Rheumatic Fever. Dr. T. Duckett Jones.
Friday, January 17 — Changes in Biologicals and in Human Reactions. Dr. Ralph E. Wheeler.
Wednesday, January 22 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.
Friday, January 24 — Parenteral Fluid Therapy for the Starving Dehydrated Patient, Infant and Adult. Dr. Allan Butler.
Wednesday, January 29 — Nasal Resistance Inhaler: A new method for the prevention and treatment of aerotitis media and aerosinusitis. Dr. H. F. Sternstein.
Friday, January 31 — Gout. Dr. Elmer C. Bartels.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, January 7, at 8:15 p.m. Dr. Leo M. Davidoff, of the Montefiore Hospital, New York City, will talk on "Recent Advances in Brain Surgery."

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, January 2, at 7:15 p.m., in the classroom of the Nurses' Residence. Dr. Edward L. Young will speak on "Gall Bladder Disease Associated with Duodenal Ulcer and Hypertension." Dr. Dorothy K. Scheidell will be chairman.

NATIONAL CONFERENCE ON MEDICAL SERVICE

The twentieth annual meeting of the National Conference on Medical Service will be held at the Palmer House, Chicago, Illinois, on February 9. Registration will commence at 9:00 a.m., and the program will include discussions in the fields of national affairs, economics and medical education. All physicians are invited to attend; there is no registration fee. Dr. Cleon A. Nafe, of Indianapolis, is president of the conference, and Dr. Creighton Barker, of New Haven, Connecticut, is secretary.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 2

THURSDAY, JANUARY 2
7:15 p.m. Monthly Clinical Conference and Meeting of the Staff. Nurses' Residence, New England Hospital for Women and Children.

FRIDAY, JANUARY 3
*9:00–10:00 a.m. Pulmonary Disease in Modern Industry. Dr. Harriet Hardy. Joseph H. Pratt Diagnostic Hospital.

MONDAY, JANUARY 6
*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

(*Notices continued on page xvii*)